Sapienza Università degli Studi di Roma

Facoltà di Medicina e Psicologia

Dottorato in Psicologia Dinamica e Clinica

XXXII ciclo

Ph.D Thesis

Predictors of clinical outcomes and Quality of Life in patients with Inflammatory Bowel Disease:

A longitudinal study

Dottoranda:

Dott.ssa Chiara Patierno

Matricola: 1739518

Tutor:

Prof. Piero Porcelli

Co-tutor:

Prof. Carlo Lai

INDEX

Introduction

Psychosomatic medicine is a wide interdisciplinary field that is concerned with the interaction of biological, psychological, and social factors in regulating the balance between health and disease (Lipowski, 1986). It provides an important conceptual framework for the scientific investigations on the role of psychosocial factors affecting individual vulnerability, course, and outcome of any type of medical disease.

Current health care is conceived as acute care, while 80% of health expenses are for chronic diseases. Almost all of health care spending is directed at biomedically oriented care. However, unhealthy behavior is responsible for over half of morbidity. Medically unexplained symptoms occur in up to 30-40% of medical patients and increase medical utilization and costs (Fava & Sonino, 2010).

Tinetti and Fried (2004) suggested that time has come to abandon disease as the primary focus of medical care. In this regard, disease-specific guidelines provide very limited indications for patients with chronic diseases. The main aim of treatment should be the attainment of individual goals and the identification and treatment of all modifiable biological and non-biological factors, according to Engel's model. The application of psychological understanding to the management of the individual patient, which includes establishing a therapeutic relationship, helping the patient to identify his/her current problems, and working with family and significant others, results to be essential in all medical settings (Porcelli, 2008).

In this context, the aim of the current thesis is to investigate the clinical role of psychological factors in patients with Inflammatory Bowel Disease (IBD). IBD is a chronic disease whose course is characterized by exacerbations and remissions that primarily affect the gastrointestinal tract. Its main clinical forms are Crohn's disease (CD) and ulcerative colitis (UC) that sharing clinical, epidemiologic, and pathogenetic features. The prevalence of IBD is around 150-200 cases per 100,000 in Western countries (Kappelman et al., 2007).

Acute episodes of IBD are characterized by clinical symptoms of severe abdominal pain and diarrhea, bloody stools, and endoscopic and histological signs of inflammation and lesions of the gut mucosa. These symptoms strongly affect various life domains (e.g., job, social and intimate relationship, hobbies) of IBD patients.

IBD patients with long-standing disease have an increased risk of developing fistulas, intestinal perforation, bowel obstruction, and colorectal cancer. Furthermore, the unpredictable course of IBD can involve a lot of complications leading to the escalation of therapy, hospitalization, and surgery (Loftus, 2004; Conley et al., 2017). The current standard of care in IBD treatment is aimed essentially at managing the inflammatory response during relapses and maintaining remission with a focus on the treatment adherence (Mowat et al., 2011; Jordan et al., 2016).

Current evidence highlights that psychological factors play a central role both in the pathophysiology and course of IBD (i.e., clinical outcome, number of relapses, pain severity) and in how patients deal with this disabling disease (adherence to the treatment, coping strategies). Moreover, some patients experience symptoms in the absence of objective evidence of disease activity, with occult inflammation, visceral hypersensitivity altered mucosal permeability, and co-existent functional disease (Gracie et al., 2016).

The first part of my Ph.D thesis aimed at analyzing the main features of this chronic medical condition. It is an overview on etiology, epidemiology, classifications, and more common medical treatments for IBD patients. The second chapter is a comprehensive review presenting "the state of the art" on the relationship between psychological factors and IBD. Finally, third and last chapter is focused on my research project. The research is a longitudinal study aimed at investigating psychological factors (i.e., anxiety, depression, somatization, perceived stress, and alexithymia) predicting/contributing to clinical outcomes (i.e. disease activity, relapse, and severity of gastrointestinal symptoms), including quality of life, of IBD patients.

Chapter 1

Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a group of idiopathic, chronic and relapsing clinical conditions that primarily affect the gastrointestinal tract. Since no specific cause for IBD is known, several hypotheses have been formulated on IBD etiology, including environmental triggers, intestinal immune mechanism, hereditable factors, gut flora, diet, mesenteric fat, medications, nicotine, infectious agents, immunization, hygiene, pregnancy, breastfeeding, stress, and lifestyle. The most validated theory supports an uncontrolled immune-mediated inflammatory response in genetically predisposed individuals to an unknown environmental trigger that interacts with the gut microbiome (intestinal flora) and primarily affects the alimentary tract (Malik et al., 2015).

IBD was considered a 'psychosomatic disease' for a long time, but this hypothesis has not been confirmed. Despite the high psychopathological comorbidity, especially anxiety and mood disorders, psychosocial factors cannot be considered to play a causative role it's the IBD etiology. IBD and IBS (irritable bowel syndrome) can be thought as examples of the dichotomy between organic and nonorganic (i.e., functional) gastrointestinal disorders, even though considerable symptom overlap is often displayed in symptom presentation (Bradesi et al., 2003; Barbara et al., 2014).

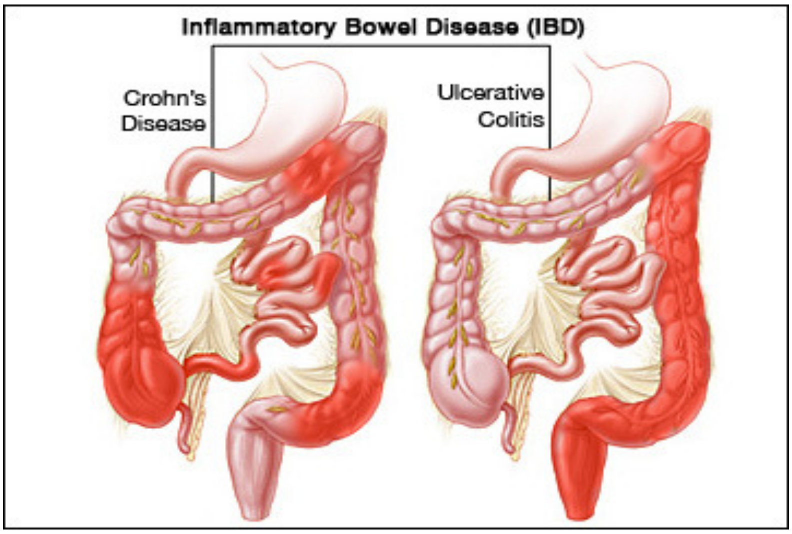
The unpredictable course of IBD can involve a lot of complications leading to the escalation of therapy, hospitalization, and surgery (Loftus, 2004; Conley et al., 2017). Its main clinical forms are Crohn's disease (CD) and ulcerative colitis (UC) characterized by overlapping clinical, epidemiologic, and pathogenetic features.

The most prevalent IBD symptoms are diarrhea, fever, reduced appetite, weight loss, abnormal stool frequency, pain, and fatigue that can also persist during clinical remission.

1.1 Ulcerative colitis

Ulcerative colitis (UC) is one of two main forms of IBD. In contrast to CD, inflammation in UC usually limited to the mucosal layer of the colon but can involve also the rectum and the more proximal portions of the colon in a continuous fashion (Figure 1) (Peppercorn et al., 2019). The age of onset is around 15-25 and 55-65 years old without differences between women and men (Steed, 2019). The most common symptoms are related to the frequency and consistency of stools. Most patients report diarrhea, rectal bleeding, mucus in the stool, tenesmus, and abdominal pain. When this symptomatology is persistent and is matched with fever, nausea, vomiting and weight loss, hospitalization can be needed. Around 10-20% of patients affected by UC suffer from extraintestinal manifestations, like arthralgia, episcleritis, and erythema nodosum, further deteriorating clinical condition (Steed, 2019).

Figure 1. CD versus UC



Because of the substantial overlapping clinical and epidemiological features of UC and CD, the accurate diagnostic classification of IBD is true challenging for clinicians. In 2003 a group of international researchers was formed to achieve a new subclassification of IBD based on recent developments. The major aim was to provide a new classification of IBD to improve diagnostic decision making in clinical practice. The results of this international group of researchers were reported at the 2005 Montreal World Congress of Gastroenterology (Silverberg et al., 2005; Satsangi et al., 2006). Regarding UC, the Montreal classification suggested two different categories:

1) Montreal classification of disease extent (Table 1);
2) Montreal classification of the disease severity (Table 2).

Table 1. Montreal classification of UC extent

Extent	Anatomy
E1 Ulcerative proctitis	Involvement limited to the rectum (that is, proximal extent of inflammation is distal to the rectosigmoid junction)
E2 Left sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3 Extensive UC (pancolitis)	Involvement extends proximal to the splenic flexure

Table 2. Montreal classification of UC severity

Severity	Definition
S0 Clinical remission	Asymptomatic
S1 Mild UC	Passage of four or fewer stools/day (with or without blood), absence of any systemic illness, and normal inflammatory markers (ESR)
S2 Moderate UC	Passage of more than four stools per day but with minimal signs of systemic toxicity
S3 Severe UC	Passage of at least six bloody stools daily, pulse rate of at least 90 beats per minute, temperature of at least 37.5°C, haemoglobin of less than 10.5 g/100mg, and ESR of at leat 30 mm/h
ESR, erythrocyte sedimentation rate	

The differential diagnosis for UC includes infectious colitis caused by bacterial, viral, or parasitic pathogens, like *Clostridium difficile infection* (Adams & Bornemann 2013; Steed, 2019), Crohn's disease and microscopic colitis (Adams & Bornemann 2013).

Diagnosis of UC is made by endoscopy with histological confirmation along with laboratory testing and radiologic imaging. Endoscopic examination aims to determine the extent of disease (E1, E2, or E3). Abdominal radiograph is employed to monitor for deterioration in acute severe colitis. Laboratory testing (c-reactive protein level, erythrocyte sedimentation rate and fecal calprotectin) sensitively detected the presence of IBD.

The main goals of treatment in these patients are to induce remission of symptoms and prevent relapse.

1.2 Crohn's disease

Crohn's disease (CD) was described for the first time from Dr. Burrill Bernard Crohn during an International Conference at New Orleans in 1932 as non-caseating granulomatous inflammation limited to the terminal ileum (Crohn et al., 1984; DeFilippis et al., 2016). To date, CD is one of the two main clinical forms of IBD. It is typically characterized by transmural inflammation of the intestine and could affect any part of the gastrointestinal tract from mouth to perianal area. All segments of the gastrointestinal tract can be affected, but the most common being the terminal ileum and colon (Torres et al., 2016). Inflammation is typically segmental, asymmetrical, and transmural. In terms of distribution of the disease 25% of the patients have colitis only, 25% have ileitis only, and 50% have ileocolitis (Gajendran et al., 2018). Diarrhea is the core symptom of CD due to decreased water absorption and increased secretion of electrolytes. Patients affected by CD frequently present with abdominal pain, fever, bowel obstruction or blood and mucus in the stools. In about 10-20%, weight loss is another clinical sign of patients with CD (Gajendran et al., 2018). One-third of patients (5-15%) with CD have perianal involvement (i.e. perianal fistula). Patients affected by Crohn's disease are at risk for early small bowel and colorectal cancer (Canavan et al., 2006; Lutgens et al., 2008). The most prevalent extraintestinal manifestations in these patients are large joint arthritis, uveitis, iritis, episcleritis, erythema nodosum and pyoderma gangrenosum.

The Montreal classification of CD based on three parameters: age at diagnosis, location, and behavior (Table 3).

Table 3. Montreal classification for CD

Age of diagnosis	A1 below 16 years old A2 between 17 and 40 years old A3 above 40 years old
Location	L1 ileal L2 colonic L3 ileocolonic L4 isolated upper disease*
Behaviour	B1 non-stricturing, non-penetrating B2 stricturing B3 penetrating p perianal disease modifier**
*L4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present. ** "p" is added to B1-B3 when concomitant perianal disease is present.	

According to Baumgart and Sandborn (2012), the diagnostic workup of CD is usually undertaken based on the following aspects:

1) Medical history: presenting symptoms, blood or mucus, or both, in stool; cramps incontinence; nocturnal diarrhea; recent intestinal infection; active or passive smoking; family history of IBD, extraintestinal symptoms.

2) Physical examination: heart rate, blood pressure, weight, body-mass index, abdominal examination, perianal inspection for fistulas, digital-rectal examination.

3) Laboratory analysis: electrolytes, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, bilirubin, transferrin, ferritin, vitamin B12, C-reactive protein, fecal calprotectin.

4) Microbial studies: stool cultures for *Clostridium difficile.*

5) Pathology and histology: at least two biopsy specimens from at least five segments including the ileum.

6) Endoscopy: ileocolonoscopy, esophagogastroduodenoscopy with biopsies (EGD).

7) Imaging studies: CT and MRI enterography or enteroclysis.

Currently, the primary therapeutic strategies have the goal of deep and prolonged remission of the CD, with particular focus on preventing complications.

1.3 Indeterminate colitis

Another subcategory of IBD approved by the Montreal classification is 'indeterminate colitis' (IC). Initially, the term indeterminate colitis was used for patients meeting all of the following criteria: patients who underwent a colectomy; patients who had disease features that were not sufficient to discriminate between CD and UC; patients whose symptoms were adequate to make a diagnosis of IBD. Later, when clinicians used the label "indeterminate colitis”, they referred to patients with evident inflammation of the colon as confirmed by clinical and endoscopic evaluations (Satsangi et al., 2006).

The recent Montreal classification recommended the use of the category ‘indeterminate colitis’ to indicate those cases where colectomy has been performed and pathologists are unable to make a definitive diagnosis of either CD or UC after full examination (Silverberg et al., 2005; Satsangi et al., 2006).

The situation is different when the clinical features consist of chronic IBD with inflammation restricted to the colon and without small bowel involvement. The endoscopy is inconclusive, and histology reveals chronic inflammation with absence of diagnostic features of either CD or UC. In these cases, the terms “Inflammatory bowel disease, type unclassified” (IBDU) should be used (Silverberg et al., 2005).

1.4 Clinical Epidemiology of IBD: incidence and prevalence in the 21st century

In the recent years, IBD has emerged as a public health challenge worldwide (Burisch et al., 2013; Ng et al., 2017) resulting in a growth of morbidity, mortality, and substantial costs to the health-care system (Rocchi et al., 2012). Since the middle of the 20th century, the incidence of IBD has increased in the Western world, which included North America, Europe, Australia, and New Zealand (Molodecky et al., 2012; Kaplan, 2015). Over 1 million residents in the USA and 2.5 million in Europe are estimated to have a diagnosis of IBD (Kaplan, 2015). Within Europe, the highest incidence and prevalence rates were found in Scandinavia and United Kingdom (Burisch et al., 2013). To date, outside the western world, the number of patients affected by IBD remains unclear (Kaplan et al., 2017), but the rising incidence of this chronic condition in newly industrialized countries could indicate an emerging epidemic of IBD also in the rest of the world, such as Asia and Eastern Europe (Burisch et al., 2013; Ng et al., 2017).

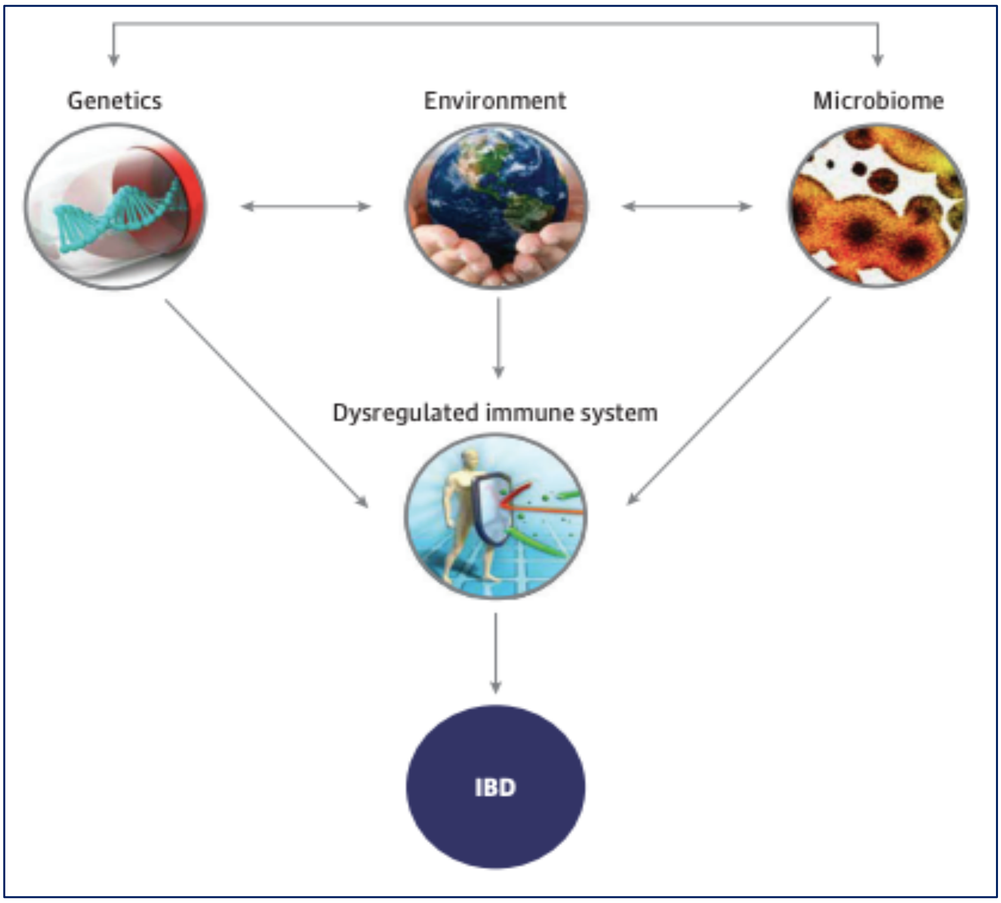
The age of onset of IBD usually is between 15 and 30 years (Peppercorn et al., 2019), though several studies suggest a possible second peak between 50 and 80 years (Bernstein et al., 2006). Shivashankar et al. (2010) stated there are differences in incidence of CD by age. Adults from 20 to 29 years have higher possibility to have a diagnosis of CD. No significant differences were found in UC.

In a study using data from the Rochester Epidemiology Project, small differences in CD and UC incidence by sex were found (Shivashankar et al., 2010). Male gender was associated with a higher incidence rate of UC compared with female sex while there is a slight female predominance in adult-onset of CD (Peppercorn et al., 2019).

1.5 IBD: etiology and pathogenesis

Recent studies increased our understanding of multiple pathways involved in IBD pathogenesis. Although the etiology of IBD remains largely unknown, it involves a complex interaction between genetics, environmental, microbial and immune factors (Figure 2) (Shouval & Rufo, 2017). The mechanisms underlying IBD onset proposed in the latest review study by Piovezani Ramos and Papadakis (2019) are based on an interplay of genetic susceptibility and environmental impact in the microbiome that through a weakened intestinal barrier can lead to aberrant and continuing immune activation responsible for the clinical and endoscopic consequences.

Figure 2. Factors involved in the aetiology of IBD (Shouval & Rufo, 2017)



1.5.1 Genetic factors

A number of studies of genetic factors implicated in the susceptibility to IBD are based on disease aggregation in twins (Baumgart & Carding, 2007). The inheritable component seems to be stronger in CD than UC, with a concordance rate in monozygotic twins of 30% to 58% in CD compared with 10% to 15% in UC (Khor et al., 2011; Piovezani Ramos & Papadakis, 2019). The risk to develop UC or CD in first-degree relatives of patients with IBD is up to 5-fold higher that in healthy people (Piovezani Ramos & Papadakis, 2019).

The relevance to identify genes and genetic loci implicated in IBD development is to improve the knowledge of disease biological pathways involved in the development of intestinal inflammation (McGovern et al., 2015).

Genome-wide association studies (GWAS)[1] showed that IBD is a polygenic disorder, characterized by multiple common genetic polymorphisms. Meta-analysis studies combining GWAS data identified 201 loci associated with IBD. Of these, 137 of 201 loci are associated with both CD and UC, while 41 are CD-specific and 20 UC-specific loci (Liu et al., 2015).

The first gene that was associated with IBD was the nucleodide-binding oligomerization domaincontaining 2 (*NOD2*) (Shaw et al., 2013*).* This gene modulates both innate and adaptive immune responses and its mutation is involved in the autophagy process in IBD (24-26). Recent progress in the genetics of IBD highlighted a significant association between IBD and the IL23R gene encoding a subunit of the receptor for the pro-infiammatory cytokine interleukin (IL-23). IL-23 is involved in the generation of Th17 cells that are implicated in the pathogenesis of IBD. Other susceptibility genes identified as immune function regulators are CARD9, IL1R2, REL, SMAD3 and PRDM1 (Zhang & Li, 2014).

More recently, studies are focusing on small intranuclear molecules that can regulate gene expression such as epigenetic markers, microRNAs, and noncoding RNAs, which have all been implicated in the pathogenesis of IBD through different pathways (Piovezani Ramos & Papadakis, 2019).

[1] In genetics, a genome-wide association study (GWA study, or GWAS), also known as whole genome association study (WGA study, or WGAS), is an observational study of a genome-wide set of genetic variants in different individuals to see if any variant is associated with a trait. In contrast, in molecular biology, SNP array is a type of DNA microarray which is used to detect polymorphisms within a population. A single nucleotide polymorphism (SNP), a variation at a single site in DNA, is the most frequent type of variation in the genome.

1.5.2 Environmental factors

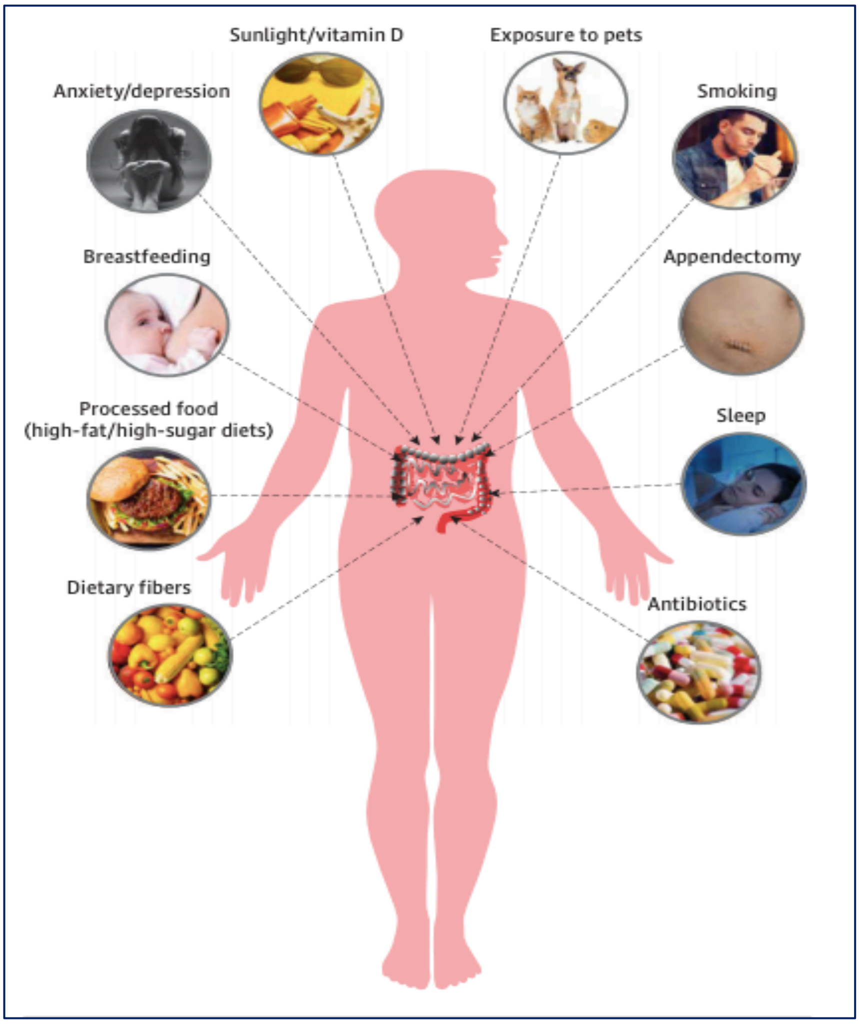
It is widely recognized that environmental factors play a crucial role in modulating the risk to develop IBD. These factors include diet, smoking, infections, appendectomy, lifestyle, early life events, pollution, and medications (Shouval & Rufo, 2017) (Figure 3).

The dietary changes of the last decades have widely contributed to the rising incidence of IBD in Western countries. Increased dietary intake of animal fat and polyunsaturated fatty acids has been correlated with an increased incidence of IBD and relapse in patients with UC (Peppercorn et al., 2019). In contrast, high intake of fiber, such as fruits and cruciferous vegetables, has been associated with a decreased risk to develop CD but no UC (Hou et al., 2011). Moreover, a higher serum level of 24-hydroxyvitamin D is also inversely related to CD risk (Ananthakrishnan et al., 2012).

A large number of studies have established the association between smoking and IBD. Cigarette smoking represents a risk factor for CD directly affecting mucosal immune responses, smooth muscle tone, gut permeability, and microvasculature (Higuchi et al., 2012). In addition, smoking might exacerbate the clinical course of CD increasing the risk for flares, surgeries, and extraintestinal manifestations like strictures and fistula (Severs et al., 2016). On the other hand, several studies suggested that current smoking has a protective effect with respect to UC (Shouval & Rufo, 2017). In these patients, smoking cessation can even lead to an increase in disease activity and risk to hospitalization.

Although no specific pathogen was identified to be directly implicated in the development of IBD, a link between infections and increasing incidence of CD and UC has been proposed. Most studies have demonstrated that salmonella and *Campylobacter* infections increase subsequent risk of developing IBD (Gradel et al., 2009). Similarly, episodes of acute gastroenteritis were associated with increased risk of IBD. Porter et al. (2008) conducted a study on a large sample including 3,000 patients with incident IBD and more than 11,000 healthy controls. They found that the risk of IBD was higher in individuals with a prior episode of acute gastroenteritis compared with controls (OR 1.4; 95% CI 1.2-1.7).

Figure 3. Environmental Factors involved in the aetiology of IBD (Shouval & Rufo, 2017)



Another potential risk factor for CD is appendectomy. The first study suggesting a correlation between appendectomy and IBD was published in 1987 by Gilat and colleagues. In this large case-control study, a significantly lower appendectomy rate was found in patients with UC compared to healthy controls, with reverse findings for CD. Most subsequent studies confirmed this correlation. Kaplan et al. (2008) stated that a considerable proportion of the risk of developing CD are observed within the first year following an appendectomy, a time when incipient CD may lead to undue appendectomies. Subsequently, the risk of CD dropped and was insignificant after 5 years. In UC, appendectomy seems to be a protective factor (Loftus, 2004). In a case-control study consisting of 212,963 patients with a previous history of appendectomy, Andersson et al. (2010) have found that the risk to UC was lower compared with controls.

Many other factors are considered involved in the development of IBD. For example, some medications, like antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for IBD since their negative consequences on intestinal mucosal (Peppercorn et al., 2019). Oral contraceptives use in premenopausal women was associated with a higher risk for both UC and CD (Cornish et al., 2008) while hormone replacement therapy represented a risk factor only for CD in postmenopausal women (Khalili et al., 2012).

Furthermore, recent ecological evidence has highlighted the important contribution of air pollution as a risk factor for IBD. Elevated air pollution is correlated with an augment in circulating polymorphonuclear leukocytes and plasma cytokines (Zhang & Li, 2014). Kaplan et al. (2010) have found that high levels of NO_2 and SO_2 in the air are associated with an increased risk of CD and UC in the UK general population.

The main perinatal and early life events supposed to be related to increased risk to develop IBD are the modes of delivery and newborn feeding. The mode of delivery (cesarean versus vaginal) can have a major impact on the composition of the intestinal microbiome influencing intestinal immune system (Salminen et al., 2004). Breastfeeding represents an important protective factor of pediatric-onset IBD (Barclay et al., 2009).

Finally, psychological factors such as stress, anxiety, and depression play a crucial role by influencing the course, prognosis and severity of IBD (Sgambato et al., 2017).

1.5.3 Immune response

IBD are characterized by an exaggerated immune response leading to destruction of gastrointestinal tissue. The development of these inflammatory diseases may be the result of an uncontrolled or inadequately upregulated cellular immune response in the intestinal mucosa towards a hitherto unknown pathogen, probably a constituent of the luminal content (Schmidt et al., 2002). The intestinal barrier, consisting of intestinal epithelial cells (IECs) and innate immune cells, contributes to maintain a balance between luminal contents and the mucosa. IECs of intestinal barrier involved different cell types including enterocytes, goblet cells, neuroendocrine cells, Paneth cells, and M cells (van der Flier & Clevers, 2009). For example, genetic deletion of Mucin 2 (Muc2), a major goblet cell-derived secretory mucin, results in spontaneous colitis in murine models (Van der Sluis et al., 2006; Piovezani Ramos & Papadakis, 2019). Another possible malfunction of immune system can be caused by development of overriding cell-mediated immune responses resulting in accumulation and activation of T lymphocytes and macrophages (Piovezani Ramos & Papadakis, 2019). Several studies have shown that these cells produce a number of T-helper-1 (Th1)-promoting proinflammatory cytokines such as interleukin (IL)-2, IL-12 and interferon-alpha (IFN-Á). These Th1 cytokines are thought to contribute to disease pathology, particularly in the development of granulomatous lesions (Schmidt et al., 2002; Uhlig et al., 2006; Piovezani Ramos & Papadakis, 2019). Intestinal homeostasis, in fact, depends on maintaining a proper balance between pro- and anti-inflammatory pathways that are mediated by TH17 and TReg cells, respectively. Improper regulation of inflammatory pathways can lead to IBD.

1.5.4 Gut Microbiome

The gut microbiome exhibits large functional diversity encoded by a collection of bacterial genes numbering more than 100 times the human gene set. It is largely recognized the connection between microbial dysbiosis and IBD. Microbial dysbiosis results from decreased diversity of the gut microbiome. In patients affected by IBD, microbial dysbiosis originates from decrease of specific anti-inflammatory bacteria such as Firmicutes, and from increase of pro-inflammatory bacteria like Proteobacteria and Bacteroidetes (Sartor et al., 2017).

To gain insight into the functional consequences of IBD-associated dysbiosis, Morgan et al. (2012) carried out a study based on novel approach pairing microbial community 16S gene sequence profiles with information from the closest available whole-genome sequences. This defined an inferred metagenome and thus complement of metabolic functional modules for each microbiome allowing to identify unique functional perturbations in the microbiomes of IBD patients. Interestingly, although the authors have identified only nine changes in bacterial clades that associated with UC (of 350, 2.6%), they classified 21 statistically significant differences in functional pathways and metabolic modules (of 295, 7.1%). This important study revealed that phylogenetically diverse changes in the composition of the GI microbiome can be functionally coordinated and lead to major modifications in the metabolic potential of the microbiota.

1.6 Epigenetics in IBD

Genetics and epigenetics are two different, though related, fields. Genetics is a branch of medicine concerned with the study of genes, genetic variation, and heredity in the organisms. Genetic testing is a type of medical test that identifies changes in chromosomes, genes, or proteins. Epigenetics is considered a relatively new area of medicine and a rapidly expanding field of research. It is the study of changes in gene function that are heritable but that do not entail a change in DNA sequence. In other words, epigenetics refers to the study of heritable changes that occur not because there is an intrinsic change in the genetic material *per se*, but because of a change in the pattern of expression of certain genes as a result of processes other than genetic mutation or recombination. Something influences the genetic code from "above" (epi-) to either shut down or induce the transcription of genetic sequences, giving rise to either biologically overactive or silent processes. The main epigenetic mechanisms include DNA methylation, histone modification, RNA interference, and the positioning of nucleosomes. Recent studies have shown that epigenetics may mediate some of the effects of environment, genetic predisposition and intestinal microbiota on IBD pathogenesis (Jenke & Zilbauer, 20012).

The epigenome can be considered as both stable and plastic. The epigenome is regarded as stable since epigenetic marks pass onto daughter cells during mitosis (Faulk & Dolinoy, 2011). However, stochastic and environmental factors can cause dynamic changes to the epigenome over time (De Santis & Selmi, 2012). During mitosis process, the level of fidelity of epigenomic replication is much lower than that of the genetic sequence (error rate of 1×10^6 for the DNA sequence compared with 1×10^3 for DNA modifications), leading to an accumulation of epigenetic changes over time (Petronis, 2010). At the same time, several environmental factors produce epimutations (epigenetic changes associated with disease). Environmental factors relevant to IBD include smoking, microbiota, and diet (Ventham et al., 2013).

First DNA methylation studies largely focused on the predisposition to cancer in IBD. DNA methylation changes in colonic epithelial cells that normally occur with aging are accelerated in IBD because of higher cell turnover in inflammation (Issa et al., 2001). Increased age-related DNA methylation, observed in colon cells of patients with colitis, could lead to genetic instability and development of cancer. Increased DNA methylation has been shown in dysplastic and surrounding nondysplastic colon tissues from patients with UC compared with control subjects or patients with UC who do not have dysplasia (Ventham et al., 2013). Four of 15 loci associated with development of cancer (*CDH1*, *GDNF*, *HPP1*, and *MYOD1*) were differentially methylated in surgical resection samples from patients with active UC compared with those with quiescent mucosa. *CDH1* encodes the cell adhesion molecule E-cadherin, which is correlated with IBD-associated cancer. Hypermethylation of the *CDH1* promoter region has been shown in dysplastic and cancerous gut tissue of patients with UC compared with nondysplastic samples (Barrett et al., 2009). The increasing interest in the role of DNA methylation in the pathogenesis of IBD has coincided with advances in platform-based DNA methylation array technologies, which have superseded candidate gene methylation profiling techniques. A study that analyzed DNA methylation in Epstein–Barr virus—transformed B cells from 18 patients with IBD versus nonaffected siblings identified 49 differentially methylated CpG sites. More than half of the differentially methylated loci contained genes that regulate immune functions, including several (*BCL3*, *STAT3*, *OSM*, *STAT5*) involved in the IL-12 and IL-23 pathways (Lin et al., 2012).

Häsler et al., (2012) studied DNA methylation in colonic tissue. An epigenome-wide association study (EWAS) of intestinal biopsy samples from 20 monozygotic twins discordant for UC identified 61 differentially methylated loci, with several containing genes that regulate inflammation (*CFI*, *SPINKK4*, *THY1*/*CD90*). This study had an interesting design in that after the loci were identified in the analysis of discordant monozygotic twins (to exclude differences in genetic factors), they were validated in an independent cohort.

To overcome the heterogeneity of cell types in tissues, a methylation-wide profiling study of whole rectal biopsy specimens from patients with active and quiescent UC and CD was validated using isolated epithelial cells from rectal biopsy specimens (Cooke et al., 2012). Many differentially methylated genes were identified in whole tissue, encoding proteins including DOK2 (involved in IL-4–mediated cell proliferation), Tap1 (a major histocompatibility complex class I transport molecule), and members of the TNF family (TNFSF4 and TNFSF12). *ULK1* was methylated only in patients with CD; its product has a role in autophagy. Genes identified as being differentially methylated in this study, replicated findings from other EWAS (Nimmo et al., 2012), and have also been identified as susceptibility genes in GWAS (Anderson et al., 2011), including *CDH1*, *ICAM3*, *IL8RA*, and *CARD9*.

The main clinical applications of epigenetics in IBD referred to the diagnosis procedure. In this regard, epigenetic research could provide biomarkers to confirm diagnosis, determine disease course, and predict response to therapy (Ushijima et al., 2006, Ventham et al., 2013). Particularly pertinent for IBD, methylation changes in *SFRP2*, measured in fecal DNA samples, have been used to identify patients with colorectal cancer with approximately 75% sensitivity and specificity (Müller et al., 2004). Biomarkers have been found in a range of body fluids, including sputum, urine, and saliva for lung, bladder, and head and neck cancers, respectively. DNA methylation is a quantitative trait and therefore an attractive biomarker. A panel of relevant hypomethylated or hypermethylated CpGs might someday be used to distinguish between UC and CD, enable disease stratification, and predict treatment response (Ventham et al., 2013).

1.7 Perspectives on current and novel treatments for IBD

The treatments of IBD has quickly evolved in the last decade. In addition to increasing available therapeutic options for patients affected by IBD, new therapeutic strategies are addressed to early diagnosis, early intervention, and tight control of biomarkers. In a recent review study, Na & Moon (2019) provided an overview of recent advances in IBD treatment options. Medications for IBD are classified in two categories: biologics and small molecule drugs. Novel biological therapies include anti-integrins, anti-cytokines, and anti-mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1). Novel small molecules drugs include Janus kinase (JAK) inibitors, small mothers against decapentaplegic homolog (SMAD) 7 antisense oligonucleotides, sphingosine-1-phosphate (SaP) receptor modulators, and phosphodiesterase (PDE) 4 inhibitors. These new biologics and small molecule drugs block immune cell communication or migration (Na & Moon, 2019).

Key points

- Inflammatory Bowel Disease (IBD) is an idiopathic, chronic, medical condition with a relapsing and remitting course, affecting the gastrointestinal tract.
- IBD including two main clinical forms: Crohn's Disease (CD) and Ulcerative colitis (UC).
- The most prevalent IBD symptoms are diarrhea, fever, reduced appetite, weight loss, abnormal stool frequency, pain, and fatigue that can also persist during clinical remission.
- The prevalence of IBD is around 150-200 cases per 100,000 in Western countries.
- The etiology of IBD involves a complex interaction between individual's genetic susceptibility, environmental, microbial and immune factors.
- Currently, the primary therapeutic strategies are mainly addressed to early diagnosis and have the goal of deep and prolonged remission of the IBD.

Chapter 2

Psychological factors affecting patients with IBD: a review of the literature

Inflammatory bowel disease is a chronic and disabling medical condition with an unpredictable course. The current standard of care in IBD treatment is aimed at managing the inflammatory response during relapses and maintaining remission with a focus on the treatment adherence (Mowat et al., 2011; Jordan et al., 2016). IBD has been long considered a classic "psychosomatic disease" and included in the famous *Holy Seven* psychosomatic diseases indicated by Alexander and his Chicago school (ulcerative colitis, rheumatoid arthritis, hyperthyroidism, hypertension, peptic ulcer, bronchial asthma, neuro-dermatitis). This notion did not receive any empirical support and IBD is considered today as a chronic multifactorial disease that is influenced, among others, by psychosocial factors throughout the different phases of the natural course of the illness (Porcelli, 2009).

Current evidence highlights that psychological factors in IBD patients play a central role both in the pathophysiology and course of IBD (i.e., clinical outcome, number of relapses, pain severity) and in how patients deal with this disabling disease (adherence to the treatment, coping strategies). Therefore, an integrating psychological intervention with conventional medical treatment results to be needed in this medical setting to reduce disease burden and disability, and to improve the well-being and quality of life of these patients.

2.1 Anxiety and depression in IBD patients

The presence of chronic medical condition (e.g., diabetes, obesity, epilepsy, asthma, inflammatory bowel disease) is often associated with higher rates of anxiety and mood disorders compared to the general population (Moussavi et al., 2007; Graff et al., 2009). Depression represents an important global public-health issue and several studies have shown that there is an increased risk of having major depression in people with one or more chronic diseases (Noel et al., 2004). Anxiety disorders, especially generalized anxiety disorder (GAD) and panic disorder, occur at a higher rate in patients with a chronic disease compared with the general population. In this medical setting, symptoms of depression and anxiety have been linked to more severe gastrointestinal symptoms and more frequent flares (Fuller-Thomson & Sulman, 2006), increased hospitalization rates (van Langenberg et al., 2010) and lower compliance with treatment (Nigro et al., 2001). Not surprisingly, anxiety and depression have a significant and negative impact on quality of life of these patients (De Jean et al., 2013).

A number of studies have investigated the relationship between anxiety and depression and IBD (Kurina et al., 2001; Mittermaier et al., 2004; Mikocka-Walus, Turnbull et al., 2007; Mikocka-Walus, Pittet et al., 2016; Graff et al., 2009; Sajadinejad et al., 2012; Jordan et al., 2016) but no causal link has been established to date. There is an open debate about the nature of this association: psychiatric symptoms precede and/or follow onset of the IBD? Several research studies suggest a reciprocal influential process, that is the experience of chronic disease is stressful to the point to trigger or intensify a psychiatric condition or, conversely, psychiatric conditions, such as anxiety and depression, may contribute to trigger or exacerbate the illness condition (Mawdsley et al., 2005).

Sajadinejad et al. (2012) suggested that patients affected by IBD reported a lot of concerns and worries about their health conditions. The awareness of incurability, the uncertain course and prognosis, the fear of surgery or development of cancer can contribute to a risk to develop anxiety symptoms in patients with a diagnosis of IBD. Moreover, according to Seligman (2002), unpredictable and incurable course of disease may impair the individual's belief about self-control and self-efficacy, thereby causing helplessness and individual vulnerability to depression.

Addolorato et al. (1997) compared 79 IBD patients with 36 healthy controls using validated symptom patient-report measures, such as State and Trait Anxiety Inventory (STAI) test and the Zung Self-rating Depression Scale, to assess anxiety and depression symptoms. IBD patients showed higher anxiety and depression levels than the control group. The percentage of subjects with state anxiety was significantly higher in the CD (62.8%; $x^2 = 11.47$, $P < 0.001$) and UC (63.9%, $x^2 = 11.10$, $P < 0.001$) groups than in control subjects (22%). There was no significant difference in trait anxiety among groups. The percentage of subjects with depression was significantly higher in the CD (41.9%; $x^2 = 7.75$, $P < 0.01$) and UC (50.0%, $x^2 = 11.06$, $P < 0.05$) groups than in control subjects (11.1%). No differences were found between CD and UC patients. In this sample, state anxiety and depression were significantly associated with physical morbidity and correlated with malnutrition in CD and UC patients.

Later, Lerebours et al. (2007) found similar results. They compared a sample consisting of 241 IBD patients with 255 blood donor community controls. Both CD and UC patients showed higher levels of depression (61% and 57%, respectively) and anxiety than controls (38%), but similar levels of depression to each other.

The prevalence of anxiety and/or depression in patients affected by IBD has been estimated to be as high as 29-35% during remission (Mittermaier et al., 2004) and more than 80% for anxiety and 60% for depression in IBD patients in active stage of disease (Addolorato et al., 1997).

In their review, Mikocka-Walus et al. (2007) identified 12 prospective studies on depression and anxiety in IBD, with samples varying from 18 to 3888, and an observation period of up to 37 months. Seven of these studies (n = 978) observed a significant positive relationship between symptoms of depression and anxiety and disease activity (Andrews et al., 1987; Lix et al., 2008; Mardini et al., 2004; Maunder et al., 2005; Mittermaier et al., 2004; Persoons et al., 2005; Porcelli et al., 1996) whereas 5 studies (n = 336) did not make this observation (Bitton et al., 2003; Langhorst et al., 2013; Lima et al., 2012; Mikocka-Walus et al., 2008; Riley et al., 1990).

The conflicting evidence in these studies may result from short-term follow-up (only in 5 studies the follow-up exceeded 1 year) and small and unrepresentative samples (6 studies with n <100) but also from different definitions and measures of depression and anxiety and measures of disease activity.

In a prospective study on the relationship between disease activity and psychological distress in patients with IBD, Porcelli et al. (1996) found that disease activity was closely paralleled by anxiety and depression levels in a clinical sample of 104 IBD patients. Overtime changes in disease activity significantly affect psychologic distress and were closely related to corresponding increases and decreases in anxiety and depression in IBD patients: improved disease was accompanied by a large increased in anxiety, and ongoing disease activity had parallel stable anxiety.

Furthermore, Mittermaier et al. (2005) showed that depressive mood associated with anxiety and impaired QoL negatively affect the course of IBD. They found that patients (28%) reporting depressive symptoms (BDI ≥ 13) showed higher anxiety, lower quality of life, more disease-related concerns and worries, and more recently perceived stress than nondepressed IBD patients. Moreover, patients with depression at baseline presented a higher probability for relapses within 18 months than patients without depression.

Häuser et al. (2011) have compared 422 IBD patients with 140 patients with chronic liver diseases (CLD) of a tertiary care center and with 422 age- and sex-matched persons of a representative sample of the general German population (GP). In this study, they showed that CD and UC patients did not differ in the levels of anxiety and depression or in the frequency of a probable mental disorder. The levels of anxiety and depression of IBD patients with active disease were higher than that of the general populations, but not of the IBD patients in remission. The depression score of the chronic liver diseases sample was higher than that of the IBD sample ($P < 0.001$), but not the anxiety score. Mental disorders were more frequent in IBD patients with slight (27.7%) and moderate/severe disease activity (49.3%) compared to GP (10.4%) ($P < 0.001$), but not in IBD patients in remission (11.3%).

Recently, Mikocka-Walus et al. (2016) have examined the relationship between symptoms of anxiety and depression and clinical recurrence in a large IBD cohort. They found a significant association between depression and clinical recurrence over time for all IBD patients. However, the relationship between anxiety and clinical recurrence over time results to be significant in patients affected by CD but not UC.

Some studies suggested that anxiety and depression can be implicated in etiology of IBD. However, most of the few studies were based on retrospective recall of symptoms which can introduce bias (Kessler, 2007; Walker et al.; 2008). Taché and Bernstein (2009) supported the idea that mood disorders can stimulate production of proinflammatory cytokines and thereby adversely affect the course of IBD. By contrast, Drossman and Ringel (2004) suggested that psychological factors, such as anxiety and depression, may modulate the clinical expression of IBD, rather than being etiologic or specific to IBD. Only Kurina et al. (2001) were able to investigate temporal relationships without potential recall bias. In this study, the authors found that patients affected by CD did not presented depression and anxiety symptoms before being diagnosed with IBD. By contrast, depression and anxiety occurred at 2 and 3 times higher rates, respectively, than expected prior to UC diagnosis. The association was strongest when onset for the psychiatric disorder was within one year of IBD diagnosis, which could reflect reactive anxiety or depressive symptoms related to early signs of IBD. A significant association was also found between depression and UC (OR = 1.49, 95% CI 1.12-1.93) when depression predated UC by more than 5 years, which is unlikely to be influenced by initial IBD symptom presentation.

Most recently, Wilkinson et al. (2019) have carried out the first study that explored the links between disease activity and emotional processing biases. The main aim of this study was to understand the mechanism underpinning the development of depression among people with IBD. Based on multivariable regression analysis, depression was associated independently with lack of social support ($\beta = 1.40$, $P < 0.05$) and increased disease activity ($\beta = 1.29$, $P < 0.05$). This study has demonstrated that less positive biases in emotional recognition could explain higher rates of depression in patients with active IBD.

In conclusion, these studies highlight the potential role of anxiety and depression in IBD patients. These patients showed a higher rate of anxiety and depressive disorders than the general population. The presence of anxiety and depression in patients with IBD represents a significant risk factor for disease exacerbation and predicts a more negative disease course. To date, however, there is no clearly evidence for anxiety and depression contributing to risk for IBD onset.

2.2 Psychological distress and IBD

Psychological distress has been defined as “a process in which environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place person at risk for disease” (Cohen et al., 1997). Many review articles have demonstrated the relationship between stress and IBD, concluding that confusions and controversies in published reports were primarily due to differences in definitions of stress (e.g. psychological distress, perceived stress, stressful life events).

Psychological distress has long been reported anecdotally to increase disease activity in IBD and recent well-designed studies have confirmed that adverse life events, chronic stress, and depression increase the likelihood of relapse in patients with quiescent IBD (Mawdsley & Ramptom, 2005).

Recent data suggest that stress-induced alterations in gastrointestinal inflammation may be mediated through changes in hypothalamic-pituitaryadrenal (HPA) axis function and alterations in bacterial-mucosal interactions, and via mucosal mast cells and mediators such as the corticotrophin releasing factor (CRF). Moreover, stress is also likely to mediate its effect on IBD through the immune system (Niess et al., 2002). To date, the therapeutic opportunities offered by stress reduction therapy remain largely unexplored, in part because of methodological difficulties of such studies. According to the stress coping model of Lazarus and Folkman (1984), the experience of stress in response to difficulties in influenced by the individual's evaluations and appraisals of the stressor and the coping strategies they use to manage it. In a recent review of the literature (Jordan et al., 2016) the role of perceived stress on adjustment outcomes was studied. The authors found a statistically significant relationship between perceived stress and a reduced quality of life ($P < .01$) increased psychological distress ($r = 0.04$, $P < .05$), anxiety ($\beta = 0.1$, $P < .01$), and depression ($\beta = 0.15$, $P < .01$). In addition, the relationship between psychological distress and perceived stress changed depending on the level of satisfaction with social support ($r = -0.014$, $P < .05$).
Recently, Sajadinejad et al. (2012) evaluated the indirect effects of psychological distress on IBD patients. They stated that stress can also indirectly affect clinical course of IBD stimulating behaviors promoting relapses (Bitton et al., 2003), inducing poor medication adherence (Nahon et al., 2011), and smoking (Singh et al., 2009).

2.3 Somatization in patients with IBD

According to Lipowski (1988), somatization is a specific individual tendency to experience and communicate somatic symptoms in response to psychological distress and to seek medical help for it. Somatization is a common problem in health care and may occur during a physical illness.

In a cross-sectional study on 185 IBD patients, Hyphantis et al. (2010) have evaluated psychological distress variables associated with quality of life (QoL) in IBD patients. Although psychological distress and disease severity are powerful predictors of QoL in IBD patients (Vidal et al., 2008), additional psychological variables, such as somatization, may also predict QoL. It is well known, for example, that functional bowel symptoms may coexist frequently with IBD, and, since anxiety can exacerbate the symptoms of irritable bowel (Simren et al., 2002), this may contribute to outcome. In this research, the authors found that somatization was significantly associated with QoL, and somatization mediated the relationship among anxiety, depression and QoL. This is probably the first study that showed an association between somatization and quality of life in IBD patients independently of anxiety and depression. It has been suggested that both the treatment of bowel disease and medical and psychiatric comorbidity are necessary to improve health-related life satisfaction in IBD patients (Janke et al., 2015). Therefore, the addition of treatment modalities focusing on somatization, such as cognitive therapy (Kroenke et al., 2007), or psychodynamic interpersonal therapy (Creed et al., 2003) may help patients with IBD to improve their QoL.

2.4 Personality and IBD

The belief that personality factors can affect vulnerability to specific disease has advanced at the early stage of development of Psychosomatic Medicine (1930-1960). In particular, psychoanalytic investigators believed that specific personality traits underlay specific ‘psychosomatic diseases’. This theory was rejected by subsequent research (Fava et al., 2010; Lipowski, 1986; Wise, 2010). The social-cognitive model of personality assumes that personality variables may deeply affect how a patient considers illness, what it means to him/her and his/her interaction with others, including medical staff (Nater et al., 2010).

Several studies have evaluated the association between personality variables and IBD. In this medical setting, the commonest personality traits reported by IBD patients were neuroticism (Moreno-Jiménez et al., 2007), perfectionism (Flett et al., 2011), and alexithymia (Carrozzino & Porcelli, 2018).

The personality trait of neuroticism refers to relatively stable tendencies to respond with negative emotions to threat, frustration, or loss (Costa & McCrae, 1992; Goldberg, 1993). Individuals in the population vary markedly on this trait, ranging from frequent and intense emotional reactions to minor challenges to little emotional reaction even in the face of significant difficulties (Lahey, 2009). Neuroticism is a robust correlate and predictor of many different mental and physical disorders, comorbidity among them, and the frequency of mental and general health service use (Fava, 1982; Ruini et al., 2003).

In a study by Moreno-Jiménez et al. (2007) neuroticism seemed to be the most closely trait associated with the QoL in a total sample of 120 patients affected by IBD. In a similar study, Boye et al. (2008) found that high neuroticism scores appear to reduce psychological wellbeing, psychological adjustment, and quality of life in IBD patients. Moreover, from linear regression analyses carried out separately for UC and CD patients, higher IBDQ score was related to less social conformity in CD and less neuroticism in UC, while higher emotional function score was related to less neuroticism in both CD and UC. By contrast, bowel function and systemic symptoms were unrelated to personality in either UC or CD.

Another personality dimension reported in these patients is perfectionism (Flett et al., 2011). The desires to succeed, set goals, and achieve these goals are all commonly revered facets of life, but the reality is that goals are often not attained, especially when they are unrealistic. For many people, failure and success can coexist throughout life in a balanced fashion without posing a problem or threatening the potential to thrive and succeed. In contrast, others place a very high premium on success and the attainment of perfection; as a result, unreasonably high standards are set and failure to meet these standards results in psychological distress. Indeed, perfectionism stemming from the self or prescribed by other people has been linked with various forms of psychological distress, including anxiety, depression, and associated mental states (Flett & Hewitt, 2002). Some researcher highlighted a significant correlation between perfectionism and psychological impact of IBD. In IBD patients, perfectionism traits were associated with negative cognitive biases, heightened reactivity to stressors, and feeling pressured to be and look perfect. The latter may be particularly detrimental for IBD patients because this medical condition is often accompanied by stigma, shame, feeling of dirty, and a burden (Hall et al., 2005; Sajadinejad et al., 2012).

Several studies found that IBD patients are characterized by another trait of personality namely alexithymia. The term “Alexithymia” was introduced by Sifneos (1973) to define an impoverished fantasy life with a resulting utilitarian way of thinking and a characteristic inability to use appropriate words to describe emotions. The inhibition of emotional expression and a life-long tendency to suppress anger have been found to involve an increased risk for a lot of health problems both using alexithymia or similar psychological constructs (Sifneos et al., 1991; Fabbri et al., 2007).

Introduced in the 1970s as a psychological characteristic of psychosomatic patients, alexithymia is to date recognized as an unspecific personality trait of vulnerability to disorders to affect dysregulation (Fabbri et al., 2007). According to Porcelli (2007), alexithymic patients may experience more severe somatic symptoms as a consequence of sustained arousal of the physiological component of emotion response systems. Moreover, alexithymic patients may also respond poorly to treatment because of their difficulties in processing emotional and somatic stimuli (Lumley et al., 1996; Taylor et al., 2000).

In a recent review of the literature, Carrozzino and Porcelli (2018) have systematically analyzed the relationship between gastrointestinal disorders (GD) and alexithymia. The first research study aimed at evaluating the presence of alexithymia in IBD patients was conducted by Porcelli et al. in the 1995. By comparing 112 IBD patients with 112 healthy controls, they found a prevalence rate of alexithymia of 35.7% in the clinical sample that was higher than the 4.5% prevalence in control subjects. In a similar study from Verissimo et al. (2000) the association between alexithymia and IBD was further confirmed. The authors reported that patients affected by IBD showed significantly higher scores than healthy controls on the TAS-20 total score (56.44±11.66 vs 48.68±9.15), DIF (20.96±6.88 vs 17.87±5.30) and EOT (20.82±4.39 vs 16.18±3.69) factors. Furthermore, Porcelli et al. (1996) confirmed that alexithymia was a stable personality trait showing, in their longitudinal study, a high correlation between baseline and 6-months follow up TAS scores ($r = 0.95$, $p < 0.001$). These findings were further supported by Verissimo et al. (1998). In their study, the alexithymia scores were not significantly correlated to the duration and the activity of IBD. By the other hand, alexithymia results to be negatively associated with IBDQ scores, particularly with bowel symptoms, systemic symptoms, and emotional functioning. In addition, Verissimo et al. (1998) found that alexithymia ($\beta = -0.27$), emotional control ($\beta = 0.26$), education ($\beta = -0.7$), and socioeconomic index ($\beta = -0.09$) played a significant role in predicting levels of QoL. In a recent study (La Barbera et al., 2017) high levels of alexithymia were associated with lower scores of physical, mental, and social functions.

Drossman and Ringel (2004) stated that alexithymia may lead IBD patients to experience and communicate their psychological distress through somatic and behavioral symptoms rather than verbal interaction with others. As consequence, IBD patients reported high levels of alexithymia displayed poorer disease outcome, lower psychological functioning, and worse health-related quality of life (Sajadinejad et al., 2012). Future studies on relationship between personality and IBD are needed.

2.5 Impact of chronic condition on Quality of Life in patients with IBD

Inflammatory bowel disease potentially affects not only negative medical outcomes but also the mental health status with additional adverse consequences on psychological well-being and QoL. QoL dimension can explain the different individual response to a standard medical treatment leading to an incomplete recovery in terms of health perception (Sonino & Fava, 2012).

QoL potentially operates as a unifying concept that comprises many domains such as general, physical, and psychological health, positive social relationships, environmental mastery, purpose in life, self-acceptance, autonomy, and personal growth factors (Bien et al., 2015; Ryff et al., 2014).

This concept was further highlighted by the World Health Organization criteria (World Health Organization, 1948), which stressed the clinical relevance to promote the health status by not only treating physical symptoms but also instilling a positive mental state (Bech et al., 2016).

Patients with IBD experience physical, emotional and social problems such as fatigue, pain, diarrhea, diminished cognitive functioning, embarrassment and anxiety or depression, which may result in limitations in social activities including employment. An important consequence is, therefore, a reduced ability to work that can have a severe negative effect on patients' QoL (Bernklev et al., 2006).

In a recent study from De Boer et al. (2016) employment status, difficulties at work and QoL in IBD patients were investigated. Out of the total sample, 123 (61%) patients were in paid employment, 31 (25%) were on sick leave, whereas 46 (23%) received a disability pension. Concentration problems (72%), low working pace (78%) and delayed work production (50%) were the most prevalent IBD-related work difficulties. The authors found that patients affected by IBD without paid employment were older and more often women, and in active stage of disease. Having no paid employment was associated with poorer QoL and more anxiety and depression symptomatology. On the other hand, IBD patients on sick leave reported statistically significantly lower scores with respect to SF-12 physical ($P < 0.001$) and mental health ($P = 0.005$) scores, IBDQ total ($P < 0.001$), bowel ($P < 0.001$), systemic ($P < 0.001$), emotional ($P = 0.001$) and social scores ($P < 0.001$), and higher HADS anxiety ($P = 0.002$) and depression scores ($P = 0.04$) compared with those not on sick leave.

Casellas et al. (2001) evaluated QoL in a sample of 289 IBD patients through IBDQ and the Psychological General Well Being Index (PGWBI). In active IBD, all dimensions of the QoL scored significantly lower than in inactive IBD, indicating a poor quality of life. Social impairment was the least impaired dimension of the IBDQ in active stage, compared with digestive and systemic symptoms. In inactive IBD, the systemic symptoms domain received the lowest score. In a subgroup of 22 patients studied before and after remission, emotional function was the most impaired dimension after achieving remission. The PGWBI was also significantly impaired in active UC and CD.

Later, Pizzi et al. (2006) evaluated QoL in 615 patients with a diagnosis of IBD using the SF-36 Health Survey. They found that IBD disease severity is the most important predictor of both physical and mental health-related quality of life in patients with this condition despite the presence of other chronic conditions.

Another recent study from Iglesias-Rey et al. (2014) highlighted that the QoL of patients with IBD, when compared with normative data from general population, is impaired in all dimensions of the IBDQ with exception of Physical Function. In a study on a Norwegian population (Bernklev et al., 2004), the impact of IBD on QoL seems to be explained not only by the physical status but also by psychological status of the patients even after taking into account such relevant variables as the presence of disease activity. Stress, anxiety and depressive symptoms have been shown to be important predictors of QoL in all the dimensions evaluated.

A very interesting study from Becker et al. (2015) has analyzed the impact of living with IBD or living with a family member suffering from IBD with regard to personal life, psychological well-being, education, career choices and financial security. As expected, more than 70% of participants indicated that IBD or living with a family member who has IBD significantly affected different areas of their lives. The most impacted aspects were participation in leisure activities, interpersonal relationships with friends, family and intimate partners, and psychological well-being. Specifically, out of 281 IBD patients, 265 reported impairment in their psychological well-being ranging from “some impact” to “major impact”. Moreover, 250 patients reported a negative impact of IBD on their interpersonal relationships and 270 declared a significant decline in leisure activities. In addition, pursuing the career of their choice and financial burden were considered to be somewhat, significantly or majorly impacted by IBD in 78% and 82% of CD and UC patients, respectively.

In conclusion, the measurement of QoL is an important parameter when one assesses the impact of chronic diseases, since the physiological changes, despite providing important information for the clinician, can cause various effects both for patients and their families, as they influence functional capacity and well-being of the patients (De Boer et al. , 2016).

2.6 Psychological interventions

Clinical Psychology included a lot of different applications, with interventions such as psychological assessment, psychological support, psychotherapy, counseling, rehabilitation psychology, neuropsychology, both in traditional clinical settings, such as public and private hospitals, and innovative clinical settings (remote outpatients’ clinics, tele-health and e-health based settings) (Castelnuovo, 2010). Already in 1956, TIME Magazine provocatively stated that medicine alone would be "a soul without psychology" and so today there is no medical area without a corresponding field in Clinical Psychology (Castelnuovo, 2010), pointing out this significative spread of psychology into clinical settings that were previously traditionally limited to bio-medical interventions.

Several research studies have shown the efficacy of psychological treatments in patients affected by a chronic disease, such as diabetes, obesity, and HIV/AIDS (de Ridder et al., 2008; Manzoni et al., 2011; Castelnuovo et al., 2015) but, to date, relatively few studies have investigated the efficacy of psychological interventions, such as psychotherapy, with IBD patients.

As discussed, psychological problems, such as somatization, anxiety, depression, are very common in patients with IBD. Even if these problems do not fulfill the criteria for a diagnosis of psychiatric disorders, psychological symptoms need to receive clinical attention from health-care services. Indeed, psychological distress can reduce the QoL and well-being of patients with IBD and may affect clinical outcome of disease. Several researchers proposed to integrate psychological treatment with conventional medical therapy, such as Niess et al. (2002). In their study, psychological interventions such as relaxation training was effective in reducing stress perceived by affecting stress-mediated alterations of the immune system. Some studies (Schwarz & Blanchard, 1991; Sibaja et al., 2007; Szigethy et al., 2004) showed that cognitive-behavioral therapy may lead to significant improvements in anxiety, depression, and QoL of IBD patients. Regarding treatment adherence, psychological interventions may increase self-efficacy and sense of personal control of these patients (Skinner, 1996).

von Wietersheim and Kessler (2006) have conducted a comprehensive review on psychotherapy with IBD patients demonstrating that psychotherapy interventions have a positive impact on the patients' mental health and help patients to cope with their illness. Two type of psychotherapy were analyzed: psychodynamic therapy (including psychoanalysis and supportive-expressive therapy) and behavior therapy, predominantly stress management training. The earliest study on this topic evaluated the effectiveness of psychotherapy in UC patients (O'Connor et al., 1964). The authors examined the effectiveness of psychoanalytic therapy on somatic factors and on mental health of 57 UC patients compared with a control group only receiving medication. Researchers concluded that the patients in the psychotherapy group did better. Some years later, in the 1987, Künsebeck and colleagues have investigated the effects of supportive psychotherapy on patients affected by CD with regard to its effect on the course of the disease and coping skills. In the therapy group, the scores for depression and anxiety decreased significantly during the study, whereas there were no differences in regard to most of the somatic symptoms. Moreover, the patients in the therapy group required significantly less inpatient or outpatient treatments or operations during the observation period than control group. In a study by Jantschek et al. (1998) the effect of psychodynamic psychotherapy on CD patients in regard to the course of the disease and to psychologic symptoms was investigated. The intervention consisted of psychodynamic psychotherapy (e.g., approximately 26 therapy sessions) and also autogenic training (approximately 17 sessions). After two years, 30% of therapy group had not experienced a relapse compared to the 23% of control group. At the same time, 29% of the control group had to undergo surgery compared to the 17% of the therapy group. As well as the study by Künsebeck et al. (1987), in regard to the somatic course of the disease, the therapy group did better than the control group but not significantly. In their study on supportive-expressive psychotherapy, Maunder and Esplen (2001) reported only reductions in maladaptive coping, not in other psychologic variables or in QoL in a group of IBD patients.

Mussell et al. (2003) studied the efficacy of cognitive behavior therapy in 28 IBD patients to reducing illness-related anxiety and stress levels and to coping with illness. The treatment consisted of psychoeducation about IBD provided by a gastroenterologist, information about how cognition and emotions generate stress, training regarding adaptive cognitive coping strategies for disease-related and routine stress, and progressive muscle relaxation training. This treatment was followed by three additional sessions every 3 months. The researchers collected data at the beginning and the end of treatment and during the follow-up sessions. Nine months after the conclusion of the therapy, the patients had lower depression scores and were better able to cope, but the latter was only significant for women. Scores for illness-related anxiety had decreased in all patients. The overall results for psychopathology and active coping had not changed during this time period.

Garcia-Vega and Fernandez-Rodriguez (2004) investigated the effectiveness of two stress management programs for CD patients by comparing three groups. The first group received 6 individual sessions of manualized stress management. The second group received a self-directed stress management program, in which the patients followed a written guidebook on stress management techniques and worked with an audiotape for home practice relaxation. The third group was the control group and received only conventional medical treatment. All patients were asked to use a personal diary to daily report symptoms of general discomfort, fatigue, diarrhea, constipation, abdominal pain, and distended abdomen. After the treatment, the patients who had received stress management training were less fatigued, less constipated, and had less abdominal pain and a less distended abdomen. The patients in the self-directed group had very similar results, whereas no significant changes were observed in the control group.

Elsenbruch et al. (2005) evaluated the effect of a “Mind-Body Therapy” on patients with UC in remission. The therapy consisted of a 60 hours training program, which included stress management training, some exercises, Mediterranean diet, behavioral techniques, and self-care strategies. Quality of life, perceived stress, and disease symptoms were assessed by using the

Short Form-36 quality of life scales (SF-36). In addition, researchers also measured disease activity, endocrine laboratory parameters, leukocytes and lymphocyte subsets in peripheral blood, and the β -adrenergic modulation of tumor necrosis factor- α production in vivo. The scores from patients in the intervention group improved in regard to some of the SF-36, but only the changes regarding the mental health scale were statistically significant. Researchers also noted significant changes in the IBD quality of life index. In contrast with these psychologic changes, however, there were no significant group differences regarding somatic data such as disease activity, endocrine, and immune parameters.

Different forms of treatment have been used (psychodynamic therapy, behavior therapy, relaxation, etc.) with IBD patients but there has not been a systematic comparison between the efficacy of various therapies. Behavioral and social interventions offer great promise to reduce disease morbidity and mortality, but as yet their potential has been relatively poorly investigated (DeLeon et al., 2003, Castelnuovo, 2010).

Because of the lack of studies and data, it is not possible to decide whether one therapy is superior to another. For this reason, future research should better investigate the role and the efficacy of psychological interventions in this medical setting.

Another important aspect regards the use of new technologies for the management and rehabilitation of chronic diseases (Castelnuovo et al., 2015). In the past years there was an increasing interest in the use of digital technologies in clinical settings, because they contribute to enhance levels of surveillance over behaviors and have the potential to provide acceptable and cost-effective interventions by transferring treatment, rehabilitation and prevention of a condition to self-care in the community (Castelnuovo et al., 2010).

The increased prevalence of chronic diseases in high-income countries is today largely attributable to the convergence of an aging population with the persistence of several risk factors, including physical inactivity, use of tobacco and alcohol, high blood pressure and cholesterol, stress, depression, and overweight and obesity. Many of these risk factors can be mitigated by health interventions and education, and communication tools, such as social media and mobile health, could support healthy lifestyle and behavior change (Castelnuovo et al., 2010; Santoro et al., 2015).

New technologies can provide clinicians and patients with many solutions in different ways: diagnostic and monitoring, early risk detection, treatment and rehabilitation, provision of feedback and alerts, and motivational strategies that facilitate changes in dysfunctional behaviors or maintenance of healthy lifestyles (Castelnuovo et al., 2015).

Telemedicine, e-health, and m-health scenarios can improve health outcomes, quality of life, and well-being and facilitate functional patient empowerment and engagement (Castelnuovo et al., 2015). Mobile health could benefit hospitalized individuals in two general ways: allowing them to more easily and reliably self-diagnose their acute symptoms, and enhancing monitoring, tracking, and communication of different biometric information for individuals with chronic medical conditions moreover enabling greater engagement and partnership in their care (Steinhubl et al., 2013).

A wide range of mobile technologies has been developed and continues to be devised to better treat individuals with other chronic conditions, including hypertension (Kumar et al., 2015), diabetes and pulmonary diseases such as asthma and chronic obstructive pulmonary disease (Steinhubl et al., 2013). In the next future, it might be useful to extend these innovative instruments also to IBD patients.

Key points

- The prevalence rate of anxiety and depressive disorders in IBD patients is estimated to be higher (up to two third of this population) than general population (ranging from 10 to 25%).
- The presence of anxiety and depression in patients with IBD may partially predict a more negative disease course.
- To date, there is no clearly evidence for anxiety and depression contributing to risk for IBD onset.
- Somatization is associated with QoL independently of anxiety and depression.
- The commonest personality traits reported by IBD patients are neuroticism, perfectionism, and alexithymia.
- Alexithymia in IBD patients was associated with poorer disease outcome, lower psychological functioning, and worse health-related quality of life.
- IBD affects negatively not only medical outcomes but also the mental health status with additional adverse consequences on QoL and well-being of the patients.
- It is recommended that clinicians routinely screen their IBD patients for these disorders in the regular course of providing care, especially at the time of first diagnosis and during disease flares.

Chapter 3

Predictors of clinical outcomes and Quality of Life in patients with
Inflammatory Bowel Disease:
A longitudinal study

3.1 Introduction

Over the past two decades, there has been increasing interest in identifying factors predicting clinical outcomes, particularly relapse/recurrence (Auzoux et al., 2019), in patients with IBD (Goldstein-Leever et al., 2019; Reddy et al., 2018). The contribution of biomarkers (Quetglas et al., 2015; Stevens et al., 2018) such as fecal calprotectin (Monteiro et al., 2019; Ricciuto & Griffiths, 2019) and c-reactive protein (Verdejo et al., 2018) has been widely investigated, but authors concluded that data are still insufficient and prospective studies evaluating the predictive role of new clinical factors, including genetic and psychological variables, are needed (Benitez & Louis, 2014). As to studies examining the predictive value of genetic factors, findings are controversial. Recently, Voskuil et al. (2019) conducted a comprehensive and critical review in this regard and concluded that further studies are required to identify genetic determinants contributing to clinical outcomes in patients with IBD. As to studies evaluating the predictive role of psychological factors, to date, as Sajadinejad et al. (2012) noted, a number of investigations have been conducted. Most of them evaluated the predictive role of psychological distress and showed that this is a triggering and exacerbating factor related to the course and symptoms of IBD (Cámara et al., 2009; Maunder & Levenstein, 2008). In other words, it was clearly demonstrated that psychological distress was one of the most important determinants of disease relapse in patients with IBD (Bitton et al., 2003; Hisamatsu et al., 2007; Mawdsley & Rampton, 2005). Other studies suggested that also affective disorders, particularly depression and anxiety, stimulate production of pro-inflammatory cytokines and thereby adversely affect the course of IBD (Kiecolt-Glaser et al., 2002; Taché & Bernstein, 2009). Recently, authors also analyzed the predictive role of quality of life (Iglesias-Rey et al., 2013; Moradkhani et al., 2013). Examining a small sample of 92 pediatric patients with IBD, Goldstein-Leever et al. (2019) showed that emotional difficulties and impaired levels of quality of life were predictive of psychology referrals. Many other psychological factors, including personality traits such as alexithymia (Porcelli et al., 1999), have been investigated. It has been reported that IBD patients with alexithymia, particularly those having greater difficulty in describing their feelings to others, have poorer disease outcomes (Flett et al., 2011; Moreno-Jiménez et al., 2007; Vaughn et al., 1999). Despite this growing literature, a consensus among researchers and clinicians is still lacking and the identification of patients at significant risk of imminent clinical relapse of IBD remains a major challenge. There is therefore an urgent need for a study providing a comprehensive assessment of biopsychosocial predictors of clinical outcomes in IBD patients.

3.2 Aims

A prospective longitudinal study with a follow up of 6 months was designed. The main aims of the present research study are to investigate:

1) the role of psychological factors (i.e., perceived stress, anxiety, depression, alexithymia, and somatization) on quality of life and on clinical outcomes of IBD patients;

2) the extent to which psychological factors can predict clinical outcomes and disease's activity in IBD patients at follow-up;

3) the extent to which psychological factors and severity of gastrointestinal symptoms can predict quality of life in IBD patients at follow-up;

4) the proportion of remitted IBD patients reporting persistent IBS-like symptoms;

5) the extent to which psychological factors are associated with overlapping IBD/IBS;

6) the role of genetic vulnerability (gene polymorphisms) in IBD patients reporting depressive symptoms.

3.3 Materials and methods

3.3.1 Study design

We performed an observational (non-interventional) longitudinal study within-subjects (no control group) with a follow-up of 6 months. Study is still on-going.

3.3.2 Variables of the study

In the current study, clinical outcomes such as disease activity (dichotomous variables: relapse/no relapse) and gastrointestinal symptoms severity (quantitative variables assessed by GSRS), and Quality of life (quantitative variables assessed by IBDQ) were the main outcome variables (dependent variables). They were evaluated at entry to the study and at 6 months of follow-up.

The main psychological predictors (independent variablese) were: anxiety, depression, somatization, perceived stress and alexithymia. They were evaluated at entry to the study and at 6 months of follow-up.

Further predictors of the research were QoL for clinical outcomes and gastrointestinal symptoms severity for QoL.

The results were corrected for sex and age (confounding variables).

3.3.3 Participants

The total sample consists of 160 outpatients affected by Inflammatory Bowel Disease recruited consecutively at the Gastroenterology and Digestive Endoscopy Unit of the University Hospital

"SS. Annunziata" of Chieti and at the Complex Gastroenterology Unit of the Hospital "Santo Spirito" of Pescara from December 2017 to April 2019. Patients had to meet the following inclusion criteria to be enrolled: (a) a clinical diagnosis of ulcerative colitis (UC) or Crohn's disease (CD) as supported by biopsies of colonic mucosa according to the diagnostic criteria of World Health Organization (WHO); (b) age between 18-75 years; (c) ability to understand and speak Italian currently.

The exclusion criteria were: (a) current severe medical comorbidity (e.g., cancer, ischemic heart disease, metabolic disease, or autoimmune disease); (b) partial or total colectomy; c) mental retardation or any cognitive deficits affecting the ability of understanding or performing the self-rating questionnaires; (d) pregnancy; (e) current major psychiatric disorders (psychosis, substance and alcohol abuse, as reported by patients and medical charts); (f) educational level < 5 years.

3.3.4 Setting

The present study was conducted during daily clinical practice in two outpatient services: the Gastroenterology and Digestive Endoscopy Unit of the University Hospital "SS. Annunziata" of Chieti and the Gastroenterology Unit of the Hospital "Santo Spirito" of Pescara. After regular medical checkup, the psychologist (C.P.) introduced the aim and the procedure of the research. All patients that fulfill inclusion criteria were invited to participate in the study. Each patient had to understand the research aims of the study and signed an informed written consent document. The participants that voluntarily accepted to participate to the study were conducted in the infirmary for the blood test. Subsequently, patients filled out the interviews (administered by the psychologist) and questionnaires in a confidential setting (designated room without any person except psychologist and patient). The duration of one single session is around 1 hours.

After six months, during a subsequent checkup to monitoring the disease activity, the psychologist asked to these patients to fill out the same questionnaires.

3.3.5 Procedures

Patients were consecutively recruited during daily clinical practice in two outpatient services: the Gastroenterology and Digestive Endoscopy Unit of the University Hospital “SS. Annunziata” of Chieti and the Gastroenterology Unit of the Hospital “Santo Spirito” of Pescara. Patients with a diagnosis of IBD were approached by the researcher assistant. After regular medical checkup, the psychologist (C.P.) introduced the aim and the procedure of the research. All IBD patients, who fulfilled inclusion criteria, were invited to participate in the study.

Patients who agreed to take part to the study and met the inclusion criteria, gave written informed consent and filled the following self-rating scales in a paper-pencil format: the Patient Health Questionnaire (PHQ), the twenty-item Toronto Alexithymia Scale (TAS-20), the Hospital Anxiety and Depression Scale (HADS), the McMaster Inflammatory Bowel Disease Questionnaire (IBDQ), the Perceived Stress Scale (PSS), and the Gastrointestinal Symptom Rating Scale – Irritable bowel syndrome (GSRS-IBS). The presence of IBS symptoms was assessed by using the Rome IV criteria for IBS (Drossman, 2016). Current psychiatric problems were evaluated through the Mini International Neuropsychiatric Interview - MINI (Sheehan et al., 1998) administered by a clinical psychologist. Moreover, a venous blood samples of all participants were collected in the EDTA-coated tubes by a nurse.

Demographic (i.e. age, gender, educational level, marital status) and socioeconomic status were collected by clinical reports.

All patients underwent clinical control examination at baseline and follow up to define the stage of disease activity. One routine endoscopic evaluation was performed during the study.

3.3.6 Measures

Demographic Information

The demographic and socioeconomic variables such as age, gender, education level, employment status, and marital status, were collected for all patients (see Appendix).

Biological measures

Biological data for evaluating inflammatory status were obtained from standard care laboratory tests included C-reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and fecal calprotectin.

C reactive protein (CRP) is a marker of acute-phase inflammatory response. It is produced mainly by hepatocytes, and its production is regulated by interleukin 6 (IL6). The CRP level can increase 10,000-fold from less than 50 μg/l to more than 500 mg/L. Its concentration can increase to 5 mg/L by 6 hours and peak at 48 hours. In healthy adults, the normal level of CRP is 0.50 mg/L.

The Erythrocyte Sedimentation Rate (ESR) is the rate at which red blood cells in anticoagulated whole blood descend in a standardized tube over a period of one hour. It is a common hematology test, and it is a non-specific measure of inflammation. In healthy adults, the normal level of ESR is ≤ 15.

Calprotectin is a protein released by a type of white blood cell called a neutrophil. When there is inflammation in the gastrointestinal tract, neutrophils move to the area and release calprotectin, resulting in an increased level in the stool. This test measures the level of calprotectin in stool as a way to detect inflammation in the intestines. In healthy adults, the normal level of Calprotectin is ≤ 50.

Clinical measures

The duration of disease and the presence of extraintestinal manifestation were collected from the patients' medical records. Clinical outcomes, such as disease and endoscopic activity were assessed by calculate specific indices to classify patients in two different groups: remission or active disease (see Appendix).

The full Mayo Score evaluates UC stage, based on four parameters: stool frequency, rectal bleeding, endoscopic evaluation and Physician's global assessment (Schroeder et al., 1987; Rutgeerts et al., 2005). The full Mayo Score ranges from 0 (normal or inactive disease) to 3 (severe activity).

The endoscopic Mayo Score (Mayo endoscopic subscore) evaluates UC stage, based only on endoscopic exploration and can be used on its own (Rutgeerts et al., 2005). The endoscopic Mayo Score ranges from 0 (normal or inactive disease) to 3 (severe activity).

Crohn's Disease Activity Index (CDAI) has been developed to assess whether or not the pathology is progressing. The index is the sum of 8 components to each of which is assigned a specific weight (Best et al., 1976). The CDAI score ranges from ≤ 150 (remission) to > 450 (severe or very severe activity).

The Simple Endoscopic Score for Crohn Disease (SES-CD) assesses the size of mucosal ulcers, the ulcerated surface, the endoscopic extension and the presence of stenosis. The SES-CD score range from 0-2 (remission) to > 15 (severe endoscopic activity).

Psychological assessment

Psychiatric syndromes

MINI International Neuropsychiatric Interview

The Mini International Neuropsychiatric Interview (MINI) was used in order to screen for the presence of axis-I comorbid psychiatric syndromes according to the Diagnostic and Statistical

Manual of Mental Disorders, 4th Edition (DSM-IV). The MINI is a short, structured diagnostic interview, with an administration time of approximately 15 min, that assesses the most important axis-I diagnoses, according to the DSM-IV and the ICD-10 (Timmerby et al., 2016). The MINI was developed to address the feasibility shortcomings of the SCID-I and CIDI (Sheehan et al., 1988). Whereas the SCID-I and CIDI can take up to 3h to administer and score, the MINI has a much shorter format. The MINI covers 17 axis I categories in a shortened format. It has good correlation with SCID-I and CIDI. The kappa values for most psychiatric diagnoses with SCID-I were 0.70 or above. Five diagnoses including current mania, current agoraphobia, obsessive–compulsive disorder, current alcohol dependence and lifetime drug dependence had kappa values between 0.60 and 0.70. Three diagnoses including current dysthymia, social phobia, and current psychotic disorder scored between 0.50 and 0.60 while current drug dependence scored 0.43. The kappa values with CIDI were 0.70 or above for most diagnoses. Four diagnoses including current and lifetime manic episode, panic disorder, current and lifetime psychotic disorder scored between 0.60 and 0.70; three diagnoses including agoraphobia, social phobia, lifetime bulimia scored between 0.50 and 0.60 and two diagnoses including generalized anxiety disorder and simple phobia scored under 0.50 (Pinninti et al., 2003).

Somatic symptoms

IBS Rome IV criteria

Because of the frequent overlap of clinical symptoms – mainly, intestinal pain, bloating, and altered bowel movements – regardless the inflammatory status of the intestinal mucosa (Spiller & Major, 2016; Barbara et al., 2014),the association between persistent functional bowel symptoms and psychological factors in IBD patients with remitted disease activity was assessed through the accepted diagnostic criteria for functional GI disorders.

The Rome IV criteria for IBS are considered the "gold standard" for diagnosing functional GI disorders and included reliable criteria for identifying the different functional disorders of the digestive tract, including IBS (Drossman, 2016). The diagnostic criteria for IBS are recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria: a) Related to defecation; 2) Associated with a change in frequency of stool.

Gastrointestinal Symptom Rating Scale - Irritable bowel syndrome (GSRS-IBS)

Gastrointestinal symptom severity was measured using the Italian version of Gastrointestinal Symptom Rating Scale – Irritable bowel syndrome (GSRS-IBS) (Svedlund, Sjodin, & Dotevall, 1988; Wiklund et al., 2003; Hunt et al., 2009) (see Appendix). The GSRS–IBS is a well-validate clinical self-rating scale for gastrointestinal symptoms that includes 13 symptoms evaluating on a 7-points scale from 1 (no discomfort at all) to 7 (very severe discomfort).

Total scores range from 13 to 91 with higher scores indicating most severe gastrointestinal symptoms.

GSRS-IBS consists of five dimensions: abdominal bloating (scores range from 3 to 21), diarrhea (from 4 to 28), constipation (from 2 to 14), pain (from 2 to 14), and fullness (from 2 to 14). Each dimension has demonstrated high internal consistency, with Cronbach's alpha ranging from .74 (pain) to .85 (satiety). The scale also demonstrates high test–retest reliability between the five factors (all r ¼ .55–.70), and good convergent validity (Wiklund et al., 2003).

Patient Health Questionnaire - 12 (PHQ-12)

The Patient Health Questionnaire (PHQ) (Spitzer et al., 1999) was designed for use in primary-care settings as a self-report measure to diagnose mental disorders, using criteria from the DSM–IV (American Psychiatric Association, 1994). PHQ-15 is a somatic symptom subscale of the PHQ full version (Kroenke et al., 2002) (see Appendix). PHQ-15 consists of 15 somatic symptoms experienced during the last 4 weeks (see Appendix). Each item is scored on a 2-point scale, in which subjects are asked to rate the severity of each symptom as 0 (“not bothered at all”), 1 (“bothered a little”), or 2 (“bothered a lot”).

When evaluating the PHQ as a screening instrument for somatization in IBD patients, we used the12-item self-rating version (PHQ-12) (Spiller et al., 2010) (see Appendix). Since three items of PHQ-15 cover common gastrointestinal symptoms of IBD, items covering GI symptoms (nausea, abdominal pain, and altered bowel habit) were removed (Aziz et al., 2015). The 12 items included: back pain, limb pain, headaches, chest pain, dizziness, fainting spells, palpitations, breathlessness, period pains, dyspareunia, insomnia and lethargy. The total PHQ-12 score ranges from 0 to 24 for women, and 0 to 22 for men (excluded item covering period pains). Somatization severity was categorized, according to total PHQ-12 score, into high (total PHQ-12 $\geq$13), medium (8-12), low (4-7) and minimal ($\leq$3) levels of somatization severity (Aziz et al., 2015).

The PHQ-12 is used as a standard instrument for assessing extra-GI somatization symptoms in these patients (e.g., Gracie et al., 2017) and showed a good internal consistency ($\alpha = 0.80$), and test–retest reliability ($r = 0.65$) (Han et al., 2009).

Alexithymia

Toronto Alexithymia Scale – 20 (TAS-20)

The twenty-item Toronto Alexithymia Scale (TAS-20) is a self-report measure considered as a “gold standard” for assessing the construct of alexithymia (Bagby et al., 1994) (see Appendix). TAS-20 is the third in the family of TAS scales, after the 26-item version (Taylor et al., 1985) and the less used TAS-Revised (Taylor et al., 1992). TAS-20 consists of 20 items grouped in three subscales: difficulty identifying feelings (F1), difficulty describing feelings (F2), and externally oriented thinking (F3). Each item is rated on a 5-point scale (from 1 = strongly disagree to 5 = strongly agree), yielding total possible scores ranging from 20 to 100. Items 4, 5, 10, 18, and 19 are reverse-worded. Although alexithymia is a dimensional construct, Parker et al. (1993) recommended to use the following cutoff scoring: < 51 for not alexithymic subjects, ≥ 51 for borderline subjects, and ≥ 61 for alexithymic subjects.

In our clinical sample, alexithymia was evaluated by an Italian translation of Toronto Alexithymia Scale – 20 (TAS-20) (Bressi et al., 1996). The Italian version of TAS-20 showed a good internal consistency (Cronbach's alpha = 0.81) and the same three-factor structure as the English version of the scale (Porcelli et al., 1995).

Psychological distress

Perceived Stress Scale (PSS)

The Perceived Stress Scale (PSS) is a brief self-report questionnaire used to assess the degree to which respondents appraise stressful situations that occurred during the past month (Cohen et al., 1983) (see Appendix). PSS consists of 14 items evaluating on a 5-points scale from 0 (never) to 4 (most often). Items 4, 5, 6, 7, 9, 10, and 13 are positively worded. Total scores range from 0 to 56 with higher scores indicating greater perceived stress.

PSS was initially developed for use in community samples and later applied with success in clinical setting, such as for IBD patients (Sewitch et al., 2001). PSS has shown adequate psychometric properties. Test–retest reliability was calculated at 2 days and 6 weeks, yielding coefficients of 0.85 and 0.55, respectively, while internal consistency in IBD sample was 0.86 (Sewitch et al., 2001).

Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a self-report measure developed by Zigmond and Snaith in 1983 to identify depression and anxiety disorders among patients in nonpsychiatric hospital clinics (see Appendix). HADS consists of two subscales: the Anxiety subscale (HADS-A) and the Depression subscale (HADS-D) both containing 7 items. Each item is rated on a 4-point scale (from 0 = not at all to 3 = most of the time), yielding total possible scores ranging from 0 to 21 for each subscale. Items 2, 4, 6, 7, 12, and 14 are reverse-worded. The cutoff scoring is the following: 0–7 for "no anxiety/depression symptoms", "8–10" for mild anxiety/depression symptoms, "11–14" for moderate anxiety/depression symptoms, and "15–21" for severe anxiety/depression symptoms (Mikocka-Walus et al., 2016). We have selected this scale since it had been broadly applied with success in IBD patients, as reported by Häuser et al. (2011) showing good psychometric properties. In this setting, its sensitivity and specificity as a screening method for mental disorder according to the criteria of the Diagnostic and Statistical Manual for Psychiatric Diseases (DSM-III-R) was 76% and 79%, respectively, with cutoff scores >8 in either HADS-subscale in IBD patients (Andrews et al., 1987). Cronbach's alpha coefficient was reported in several studies (Bjelland et al., 2002) and varied for HADS-A from .68 to .93 (mean .83), and for HADS-D from .67 to .90 (mean .82). Finally, when compared to other questionnaires for anxiety and depression in common use such as BDI, STAI, and SCL-90 Anxiety and Depression subscales, the correlation to HADS-D and HADS-A, respectively, were between .60 and .80, showing a very good concurrent validity of HADS.

Quality of life

Inflammatory Bowel Disease Questionnaire (IBDQ)

The McMaster Inflammatory Bowel Disease Questionnaire (IBDQ) is the most used self-report instrument assessing health-related quality of life in patients with IBD (Mitchell et al., 1988). IBDQ comprises 32 items covering four dimensions: bowel symptoms (10 items), emotional health (12 items), systemic symptoms (5 items), social function (5 items) (Ciccocioppo et al., 2011). Each item is rated on a 7-point scale (7 = the best function and 1 = the worst). The total IBDQ score ranges from 32 to 224 with a higher score showing a better QoL. In addition, average per item scores can be calculated for each of the 4 areas evaluated. It was developed in English speaking countries and its application in clinical trials has progressively increased, thus highlighting the need for its translation into various languages, including Italian. The Italian version of IBDQ (Ciccocioppo et al., 2011) has shown good psychometric properties with an overall Cronbach's alpha of 0.96 for the IBD cohort of patients. Item internal consistency was satisfied for 100% of patients, while discriminant validity showed a few items with higher correlations with other scales. Test–retest correlations indicated good reliability (r = 0.81).

3.3.7 Genotyping analysis

Patients were genotyped for 3 polymorphisms: *BDNF* (Brain-derived neurotrophic factor); *HTR2A* (gene encoding 5-hydroxytryptamine (serotonin) receptor 2A); *TPH2* (tryptophan hydroxylase-2 gene).

Whole blood (12 mL) was drawn from each participant by venipuncture into EDTA-containing tubes. Genomic DNA was isolated from 200 µL of whole blood using MagPurix, Blood DNA extraction Kit (12sZinexts Life Science Corp.- CodZP01001).

For rs6265 c.220G>A, rs6311 -988G>A, rs457062 -703G>T (Assay ID: C__11592758_10, C__8695278_10, C___226207_10), genotyping was performed using TaqMan SNP Genotyping Assay (Applied Biosystem; Foster City, CA, USA). PCR was carried out on a QuantStudio 5 Real- Time PCR System (Applied Biosystem; Foster City, CA, USA) in a 25ul volume using TaqPath ProAmp Master Mix and 10ng of DNA. Initial enzyme activation was carried out at 95°C for 10 min., followed by 40 cycles at 92°C for 15 s and 60°C for 1 min.

3.3.8 Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., version 16, Chicago, IL). Descriptive analyses were performed with all sociodemographic, clinical, and psychological variables. Mean and standard deviations (SD) were calculated for parametric data, and medians (ranges) for non-parametric data. Differences between patients were sought using analysis of variance (ANOVA), Student's t-test, or chi-squared, as appropriate. Univariate analyses were conducted using Pearson's correlation coefficients. A series of logistic and linear regression analysis were also performed to identify the risk factors associated to the worst clinical condition. The significance level was set at $p < 0.05$, 2-tailed. Effect size statistics were computed using the mean difference in scales scores (patients versus participants) divided by their pooled standard deviations. An effect size higher than 0.40 was considered borderline (Arnold, 2011), whereas an effect size of 0.80 or higher was considered clinically significant (Cohen, 1988). The effect size statistics as a provisional answer to the clinical question "how much" are not limited to detect simply the presence or absence of a statistically significant difference as a p-value does, but it provides more important clinical information enabling clinicians to account for the degree of an effect (Carrozzino et al., 2018).

For the genetic testing, deviation from the Hardy-Weinberg equilibrium was performed using the correspondent x^2 procedure for gene polymorphisms.

3.4 Ethical issues

The research study received the approval by the Institutional Review Board of the University "Gabriele d'Annunzio" of Chieti-Pescara, Chieti, Italy (Prot. n.254 of 03/14/2017). The study was carried out in accordance with the Declaration of Helsinki. The data were analyzed anonymously according to the Italian law on the treatment of personal data (i.e., Law no. 196, June 30, 2003). All participants had to provide and sign a written informed consent including a privacy protection disclaimer (see Appendix).

3.5 Results

Participant Characteristics

Of the 171 patients who met the inclusion criteria, 160 agreed to participate, yielding a response rate of 93.6%. Of the total sample, 112 (70%) had a diagnosis of UC and 48 (30%) had a diagnosis of CD. At baseline, the majority of the patients (71.9%) were in the active stage of the disease from mild to severe, while the 28.1% were in remission. Extraintestinal manifestations, such as joint arthritis, arthralgia, episcleritis, erythema nodosum, perianal fistulas, and psoriasis were reported by 33.8% of the total sample. The 25.6% reported psychiatric syndromes, like anxiety and depressive disorders. The most prevalent psychiatric conditions were depression (12.5%) and anxiety (11.9%). The clinical characteristics of the patients at baseline and at follow-up are shown in Table 1.

The participants were predominantly men (60.6%) with a mean age of 46.5 years (*SD* ± 15.71). Most of the subjects (48.1%) had graduated from high school and resulted to be currently employed (40.9%) and married (55%). The clinical and demographic characteristics of the patients are shown in Table 2.

The sample size at follow-up was relatively small (n = 90, 56.3%) since at this time the study recruitment is still open for achieving the sample size objective. However, baseline and follow-up samples had similar demographic and clinical characteristics.

Table 1. *Clinical characteristics of the sample at baseline and T1 (6 months).*

	Baseline (n =160)	T1 (n = 90)
	N (%)	N (%)
Disease		
Ulcerative colitis	112 (70)	59 (65.6)
Crohn's disease	48 (30)	31 (34.4)
Disease activity		
Quiescent	45 (28.1)	31 (34.5)
Mild	45 (28.1)	27 (30)
Moderate	47 (29.4)	29 (32.2)
Severe	23 (14.4)	3 (3.3)
Endoscopic evaluation		
Quiescent	36 (23.1)	23 (26.1)
Mild	36 (23.1)	21 (23.9)
Moderate	42 (26.9)	25 (28.4)
Severe	42 (26.9)	19 (21.6)
Extraintestinal manifestation	54 (33.8)	32 (35.6)
Psychiatric syndromes	41 (25.6)	23 (25.6)
Major depression	20 (12.5)	12 (13.3)
Dysthymia	3 (4.8)	2 (2.2)
Suicidal ideation	3 (4.8)	2 (2.2)
PTSD	2 (1.3)	-
Agoraphobia	4 (2.5)	3 (3.3)
Obsessive-compulsive disorder	1 (0.6)	1 (1.1)
Social phobia	1 (0.6)	1 (1.1)
Panic disorder	13 (8.1)	8 (8.9)
Generalized anxiety disorder	19 (11.9)	8 (8.9)

__Table 2.__ Demographic characteristics of the sample at baseline and T1 (6 months).

	IBD sample at baseline (n =160)	IBD sample at T1 (n = 90)
	N (%)	N (%)
Gender		
Male	97 (60.6)	56 (62.2)
Female	63 (39.4)	34 (37.8)
Marital status		
Unmarried	43 (26.9)	30 (33.3)
Coliving	10 (6.3)	5 (5.6)
Married	88 (55)	42 (46.7)
Separated/Divorced	13 (8.1)	11 (12.2)
Widow/Widower	4 (2.4)	2 (2.2)
Single	2 (1.3)	0 (0)
Employment		
Employed	65 (40.9)	39 (43.3)
Unemployed	16 (10.1)	8 (8.9)
Housewife	13 (8.2)	6 (6.7)
Retired	29 (18.2)	17 (18.9)
Student	13 (8.2)	8 (8.9)
Self employed	23 (14.5)	12 (13.3)
Educational Level		
Primary school	10 (6.3)	1 (1.1)
Middle school	36 (22.2)	23 (25.6)
High school	77 (48.1)	46 (51.1)
Bachelor’s degree	14 (8.8)	9 (10)
Master’s degree	17 (10.6)	8 (8.9)
Ph.D or Specialization	5 (3.1)	3 (3.3)
	Mean (SD)	Mean (SD)
Age	46.54 (15.71)	45.21 (16.04)

Descriptive analysis

In Table 3, means, standard deviations (SD), and medians of the self-report questionnaires of the total sample are shown. At baseline, IBD patients reported moderate gastrointestinal symptoms (GSRS total scale = 32.91±14.79), particularly "diarrhea" (12.48±6.75), "pain" (5.08±2.96), and "abdominal bloating" (8.41±4.34).

Our clinical sample reported moderate anxiety/depression symptoms by HADS total scores (14.23±7.28), moderate perceived stress by PSS (22.87±8.36), and low levels of somatization (6.33±3.78).

As to IBD scores (156.88±38.33) on QoL, the most compromised areas were "bowel symptoms" (50.65±12.65), "emotional health" (58.56±13.54), and "social function" (26.31±8.37).

Changes in scale scores from baseline to the 6-month follow-up evaluation were not significantly different, except for the TAS-20 subscale on DDF. At follow-up, IBD patients reported lower difficulties in describing feelings.

Table 3. Mean scores and standard deviations of self-rating scales at baseline and at follow up.

	Min	Max	Mean Baseline N = 160	SD	Median Baseline	Min	Max	Mean Follow-up N = 90	SD	Median Follow-up	t	p
GSRS-IBS TOT	13	71	32.91	14.79	30.00	13	69	31.39	12.99	29.50	1.055	.292
GSRS-IBS Pain	2	12	5.08	2.96	4.00	2	11	4.79	2.74	4.00	.945	.346
GSRS-IBS Abdominal bloating	3	21	8.41	4.34	7.00	3	21	8.19	3.97	7.00	.392	.696
GSRS-IBS Constipation	2	10	3.29	2.00	1.98	2	10	3.18	1.73	2.00	.464	.643
GSRS-IBS Diarrhea	4	27	12.48	6.75	11.00	4	28	11.49	6.25	10.00	1.145	.253
GSRS-IBS Fullness	2	12	4.06	2.81	2.00	2	14	3.81	2.56	2.50	.701	.484
PHQ	0	18	6.33	3.78	6.00	0	15	5.98	3.58	6.00	.711	.478
HADS Anxiety	0	21	6.61	4.4	6.00	0	18	6.11	4.67	6.00	.835	.405
HADS Depression	0	21	7.63	3.86	7.00	0	19	7.34	3.89	7.00	.549	.583
HADS Total	0	42	14.23	7.28	13.00	1	36	13.40	7.78	13.00	.845	.399
PSS	0	51	23.87	8.36	24.00	2	52	22.47	8.32	23.00	1.428	.154
IBDQ Total	32	221	156.88	38.33	162.00	11	70	162.20	38.91	174.00	1.106	.270
IBDQ Bowel Symptoms	15	70	50.65	12.65	51.00	11	70	52.39	12.88	56.00	1.108	.269
IBDQ Systemic Symptoms	7	35	22.63	6.91	22.63	6	36	22.41	6.93	23.50	.149	.882
IBDQ Emotional Health	21	83	58.56	13.54	60.00	19	82	59.48	14.71	62.50	.515	.607
IBDQ Social Function	5	35	26.31	8.37	29.00	6	35	27.92	8.37	31.00	1.523	.129
TAS-20	20	83	45.08	12.99	44.00	20	80	43.43	13.77	42.00	1.292	.198
TAS-20 DIF	7	35	14.36	6.20	13.00	7	32	13.97	6.36	13.00	.796	.427
TAS-20 DDF	5	25	11.83	5.23	11.00	5	25	10.58	4.89	10.50	2.078	.039
TAS-20 EOT	8	38	18.89	5.37	18.00	8	32	18.66	5.70	18.00	.321	.748

As shown in Table 4, 25% of the total sample reported anxiety symptoms (11.22 ± 3.47) as measured by the anxiety subscale of HADS using a cut-off of ≥8. Almost half of our sample (46.9%) had depressive symptoms according to HADS "Depression" subscale (10.69 ± 2.96) using a cut-off of ≥8. Moreover, 26.9% of patients resulted to be alexithymic (61.65 ± 9.41) using a large cut-off of ≥ 51 (borderline to definite alexithymia). Instead, when considering the alexithymia score as a continuous scale, total scores of our clinical sample (45.1±12.99) were quite similar to the Italian general population (44.7±11.3). Only the factor 3, EOT (externally oriented thinking) was found to be higher (18.9±5.37) than Italian general population (17.1±4.9) (Bressi et al.,1996).

Table 4. *Differences between mean scores of self-rating scales (categorial approach) at baseline.*

	N (%)	Mean	DS	*t*	*p*
HADS Anxiety					
No Anxiety	102 (75.0)	3.98	2.13	14.42	.000
Anxiety	58 (25.0)	11.22	3.47		
HADS Depression					
No Depression	85 (53.1)	4.92	2.16	13.92	.000
Depression	75 (46.9)	10.69	2.96		
TAS-20					
No Alexithymic	117 (73.1)	38.99	7.84	15.34	.000
Alexithymic	43 (26.9)	61.65	9.41		

Table 5 shows means and standard deviations of inflammatory markers at baseline. Half of the sample had higher levels of general inflammation: 67 (43.8%) patients had a value superior or equal to 15 (37.51±19.18) at ESR indices and 79 (51%) patients had a value equal or superior to 0.50 at PCR (12.24±19.16). Most of half of the sample (71%) showed high level of fecal calprotectin (828.30±410) indicating the presence of severe inflammation in the lower gastrointestinal tract.

Table 5. *Mean scores of inflammatory markers at baseline*

	N /%)	Min	Max	Mean	DS	Median
ESR	153 (95.6)	1	88	20.15	20.08	11
ESR ≤ 15	86 (56.2)	1	15	6.62	3.48	6
ESR > 15	67 (43.8)	16	88	37.52	19.18	34

	N /%)	Min	Max	Mean	DS	Median
PCR	155 (96.9)	-3.23	88	20.15	20.08	11
PCR ≤ 0.50	76 (49)	-3.23	0.50	-1.52	1.58	-.33
PCR > 0.50	79 (51)	0.52	138	12.24	19.16	5.96

	N /%)	Min	Max	Mean	DS	Median
Calprotectin	142 (88.7)	1	3451	596.61	898.08	213.5
Calprotectin ≤ 50	41 (28.9)	1	49	25.85	11.67	25
Calprotectin > 50	101 (71.1)	59	3451	828.30	410	596

Table 6 shows means and standard deviations of inflammatory markers at follow-up. Less of half of the sample had higher levels of general inflammation: 26 (34.2%) patients had a value superior or equal to 15 (35.59±19.18) at ESR indices and 35 (48%) patients had a value equal or superior to 0.50 at PCR (24.73±74.58). Most of half of the sample (71%) showed high level of fecal calprotectin (502.80±673.44) indicating the presence of severe inflammation in the lower gastrointestinal tract.

Table 6. *Mean scores of inflammatory markers at follow-up*

	N /%)	Min	Max	Mean	DS	Median
ESR	76 (84.4)	2	112	16.66	19.94	8
ESR ≤ 15	50 (65.8)	2	14	6.3	3.05	6
ESR > 15	26 (34.2)	16	112	35.59	19.18	27.5

	N /%)	Min	Max	Mean	DS	Median
PCR	73 (81.1)	-3.23	433	11.27	52.88	.44
PCR ≤ 0.50	38 (52)	-3.23	0.46	-1.13	1.45	-.29
PCR > 0.50	35 (48)	0.59	433	24.73	74.58	5.38

	N /%)	Min	Max	Mean	DS	Median
Calprotectin	73 (81.1)	-50	3496	350.58	608.09	125
Calprotectin ≤ 50	22 (30.1)	-50	49	-2.32	35.53	-6
Calprotectin > 50	51 (69.9)	60	3496	502.80	673.44	202

Comments:

Our preliminary analysis shows that:

1) The sample of our study consists predominantly of patients with a diagnosis of UC (70%).

2) Most of the participants were middle-aged men (60.6%, 46.5 years ± 15.71 years-old).

3) At baseline, the majority of patients (71.9%) were in the active stage of the disease from mild to severe, while the 28.1% in remission.

4) A quarter (25%) of patients reported anxiety symptoms and almost half (46.9%) depressive symptoms.

5) Our IBD patients presented moderate perceived stress (22.87±8.36), and low levels of somatization (6.33±3.78).

Associations between psychological factors, somatic symptoms, and inflammation

The correlation matrix between inflammatory markers and gastrointestinal symptoms severity is reported in Table 7. ESR correlated positively with GSRS total scale ($r = .22$, $p < .05$), abdominal bloating ($r = .21$, $p < .05$), and diarrhea ($r = .19$, $p < .01$), although in the small range of association. Fecal calprotectin correlated positively with GSRS in the moderate range for total scale ($r = .34$, $p < .05$), pain ($r = .25$, $p < .05$), and diarrhea ($r = .44$, $p < .05$), and weakly with fullness ($r = .18$, $p < .01$). In contrast, there was no significant relationship between gastrointestinal symptoms severity and PCR.

Table 7. Correlations between inflammatory markers and GSRS.

	GSRS-IBS Total Score	GSRS-IBS Pain	GSRS-IBS Abdominal bloating	GSRS-IBS Constipation	GSRS-IBS Diarrhea	GSRS-IBS Fullness
ESR	**.22****	.13	**.21****	.06	**.19***	.12
PCR	.06	.09	-.03	.11	.07	-.02
Fecal calprotectin	**.34****	**.25****	.13	-.02	**.44****	**.18***

**p < .01*

***p < .05*

The correlations between inflammatory markers and psychological factors symptoms are shown in Table 8. Only ESR has been found to be positively and significantly correlated with all psychological variables although at low level, except for TAS-20 total score and its two subscales DDF and EOT.

Table 8. Correlations between inflammatory markers and Psychological factors.

	PSS	PHQ	HADS Anxiety	HADS Depression	HADS Total score	TAS-20 DIF	TAS-20 DDF	TAS-20 EOT	TAS-20 Total score
ESR	**.18***	**.25****	**.16***	**.21****	**.21***	**.22****	-.02	-.05	.07
PCR	-.02	.13	.02	.09	.06	-.01	-.07	-.02	-.04
Fecal calprotectin	-.06	.04	.05	.07	.07	.02	-.01	-.01	.00

**p < .01*

***p < .05*

Table 9 shows the correlations between inflammatory markers and quality of life in IBD patients. ESR and Fecal calprotectin are negatively and significantly correlated with IBDQ total scale and all four subscales. In contrast, no correlation was found between PCR and quality of life.

Patients with higher levels of general inflammation (particularly ESR and calprotectin) showed therefore a tendency to report also higher level of psychological distress, such as anxiety, depression, somatization, and perceived stress as well as poorer quality of life.

Table 9. Correlations between inflammatory markers and IBD Quality of life (IBDQ).

	IBDQ Total score	IBDQ Bowel symptoms	IBDQ Systemic symptoms	IBDQ Emotional health	IBDQ Social function
ESR	**-.27****	**-.17***	**-.31****	**-.34****	**-.28****
PCR	-.07	-.06	-.05	-.05	-.16
Fecal calprotectin	**-.24****	**-.31****	**-.19***	**-.17***	**-.31****

**p < .01*

***p < .05*

The correlations between GSRS and psychological factors are illustrated in Table 10. Gastrointestinal symptoms severity (GSRS total scores) was positively and significantly ($p < .05$) correlated at a higher level with perceived stress ($r = .33$), somatization ($r = .42$), and anxiety (r = .42), and, at a smaller extent, with depression (.28), and ability to identify emotional feelings (r = .26). All five subscales of GSRS have been found to be positively and significantly correlated with these psychological variables. No significant correlations were found between gastrointestinal symptoms severity and TAS-20, DDF, and EOT.

As it might be expected, patients with more severe gastrointestinal symptoms reported higher levels of psychological distress, such as somatization, anxiety and depression, and more difficulty to identify emotional feelings.

Table 10. Correlations between gastrointestinal symptoms severity (GSRS) indices and Psychological factors.

	PSS	PHQ	HADS Anxiety	HADS Depression	HADS Total score	TAS-20 DIF	TAS-20 DDF	TAS-20 EOT	TAS-20 Total score
GSRS-IBS Total Score	**.33****	**.42****	**.42****	**.28****	**.40****	**.26****	-.03	-.12	.06
GSRS-IBS Pain	**.25****	**.33****	**.32****	**.19***	**.29****	**.24****	-.07	-.1	.04
GSRS-IBS Abdominal bloating	**.25****	**.39****	**.37****	**.25****	**.35****	**.24****	-.00	-.1	.07
GSRS-IBS Constipation	**.17***	**.24****	**.16***	**.18***	**.19***	.11	.11	-.01	.09
GSRS-IBS Diarrhea	**.28****	**.30****	**.31****	**.25****	**.32****	**.19***	-.08	-.09	.02
GSRS-IBS Fullness	**.22****	**.29****	**.39****	**.12**	**.30****	**-19***	.02	-.12	.05

**p < .01*

***p < .05*

Patients with more severe gastrointestinal symptoms reported also lower levels of quality of life. The correlations between GSRS and quality of life are presented in Table 11. Gastrointestinal symptoms severity (GSRS total scores) results to be negatively and significantly (p < .05) correlated with IBDQ total score (r = -.72), bowel symptoms (r = -.81), systemic symptoms (r = -.57), emotional health (r = -.67), and social function (r = -.68). Out of

5 subscales of GSRS, 4 (pain, abdominal bloating, diarrhea, and fullness) showed high correlations with IBDQ.

Table 11. Correlations between gastrointestinal symptoms severity (GSRS) and IBD Quality of Life (IBDQ).

	IBDQ Total score	IBDQ Bowel symptoms	IBDQ Systemic symptoms	IBDQ Emotional health	IBDQ Social function
GSRS-IBS Total Score	**-.72****	**-.81****	**-.57****	**-.67****	**-.68****
GSRS-IBS Pain	**-.62****	**-.71****	**-.48****	**-.54****	**-.57****
GSRS-IBS Abdominal bloating	**-.56****	**-.66****	**-.46****	**-.53****	**-.49****
GSRS-IBS Constipation	-.11	-.09	-.09	-.10	-.12
GSRS-IBS Diarrhea	**-.67****	**-.76****	**-.5****	**-.62****	**-.67****
GSRS-IBS Fullness	**-.49****	**-.51****	**-.46****	**-.48****	**-.4****

*$p < .01$

**$p < .05$

Patients with higher levels of alexithymia and psychological distress, such as somatization, anxiety, and depression, had poorer quality of life. The most impaired areas were systemic symptoms and emotional health. Table 12 shows the correlations between psychological factors and quality of life in IBD patients. All the correlations were negative and significant with a $p < .05$. Only correlation between DDF subscale of TAS-20 and subscale “Emotional health” of IBDQ results significant with a $p < .01$.

Except for DDF and emotional health, no significant correlations were found between quality of life and subscales DDF and EOT of TAS-20.

Table 12. Correlations between Psychological factors and IBD Quality of Life (IBDQ).

	IBDQ Total score	IBDQ Bowel symptoms	IBDQ Systemic symptoms	IBDQ Emotional health	IBDQ Social function
PSS	**-.37****	**-.25****	**-.48****	**-.49****	**-.32****
PHQ	**-.50****	**-.43****	**-.65****	**-.57****	**-.38****
HADS Anxiety	**-.45****	**-.37****	**-.55****	**-.59****	**-.31****
HADS Depression	**-.37****	**-.27****	**-.45****	**-.45****	**-.37****
HADS Total score	**-.47****	**-.37****	**-.57****	**-.59****	**-.39****
TAS-20 DIF	**-.41****	**-.31****	**-.38****	**-.50****	**-.39****
TAS-20 DDF	-.12	-.01	-.09	**-.19***	-.05
TAS-20 EOT	-.04	.05	-.02	.04	-.06
TAS-20 Total score	**-.26****	**-.13****	**-.22****	**-.29****	**-.23****

**p < .01*

***p < .05*

Table 13 presents the correlations between psychological variables within this group of IBD patients. As expected, psychological variables were positively and strongly associated between them.

Table 13. Correlations between Psychological factors in IBD patients.

	PSS	PHQ	HADS Anxiety	HADS Depression	HADS Total score	TAS-20 DIF	TAS-20 DDF	TAS-20 EOT	TAS-20 Total score
PSS	-	.44**	.66**	.51**	.67**	.39**	.26**	.01	.29**
PHQ	.44**	-	.50**	.49**	.50**	.36**	.12	-.02	.21**
HADS Anxiety	.66**	.56**	-	.55**	.89**	.50**	.27**	-.04	.33**
HADS Depression	.51**	.28**	.55**	-	.86**	.49**	.31**	.12	.41**
HADS Total score	.67**	.48**	.89**	.86**	-	.57**	.33**	.04	.42**
TAS-20 DIF	.39**	.36**	.50**	.49**	.57**	-	.53**	.32**	.82**
TAS-20 DDF	.26**	.10	.27**	.31**	.33**	.53**	-	.35**	.79**
TAS-20 EOT	.01	-.03	-.04	.12	.04	.32**	.35**	-	.70**
TAS-20 Total score	.30**	.20*	.33**	.41**	.42**	.82**	.79**	.70**	-

*$p < .01$

**$p < .05$

Comparison between men and women at baseline

Table 14[2] shows that women reported more abdominal bloating ($t = 2.98$, $p = .004$), and fullness ($t = 2.52$, $p = .013$) than men. Moreover, women had significantly higher levels of anxiety and depression ($t = 2.59$, $p = .011$), somatization ($t = 4.31$, $p < .001$), and perceived stress ($t = 2.04$, $p = .043$) than men. Unlikely, men had worse emotional health ($t = 2.38$, $p = .018$) than women. Correlations between age and psychological variables were also performed and resulted to be not significant.

[2] For readability purposes, Table 14 reports only scale scores showing significantly between-gender differences. The complete set of data is available upon request.

__Table 14.__ Comparison between men and women patients at baseline

	Mean	DS	*t*	*p*	*d*
GSRS-IBS Abdominal bloating					
Men	7.56	3.72	2.98	.004	0.25
Women	9.71	4.90			
GSRS-IBS Fullness					
Men	3.59	2.35	2.52	.013	0.21
Women	4.79	3.29			
PSS					
Men	22.79	7.76	2.04	.043	0.16
Women	25.52	9.04			
PHQ					
Men	5.34	3.45	4.31	.000	0.35
Women	7.84	3.79			
HADS Anxiety					
Men	5.66	3.47	3.21	.002	0.28
Women	8.06	5.25			
HADS Total score					
Men	12.96	5.94	2.59	.011	0.22
Women	16.19	8.65			
IBDQ Emotional health					
Men	60.59	12.69	2.38	.018	0.17
Women	55.94	14.28			

Comparison between patients with and without a psychiatric diagnosis

Patients with one or more psychiatric syndromes as assessed through MINI, reported higher levels of psychological distress and somatic symptoms and poorer quality of life than patients without psychiatric syndromes (Table 15[3]). Specifically, these patients reported more severe gastrointestinal symptoms at GSRS total score (t = 2.43, p = .016), and in subscales of pain (t = 2.66, p = .009), abdominal bloating (t = 2.25, p = .026), and fullness (t = 2.45, p = .015).

As expected, patient had one or more psychiatric syndromes reported significantly high levels of anxiety and depression (t = 5.60, p < .001), somatization (t = 2.90, p = .005), and perceived stress (t = 5.22, p < .001). Furthermore, they had more difficulty to identify feelings and distinguish between feelings and bodily sensations (t = 5.31, p < .001), and to describing feelings (t = 2.99, p = .003).

Moreover, these patients had poorer QoL, showed lower scores particularly in subscales of systemic symptoms (t = 5.03, *p* < .001), emotional health (t = 5.49, *p* < .001), and social function (t = 2.64, *p* = .009).

[3] For readability purposes, Table 15 reports only scale scores showing significantly differences. The complete set of data is available upon request

Table 15. *Comparison between patients with and without psychiatric syndromes*

	Mean	DS	*t*	*p*	*d*
GSRS Total score					
No psychiatric syndromes	31.72	14.03	2.43	.016	0.22
Psychiatric syndromes	37.98	14.68			
GSRS Pain					
No psychiatric syndromes	4.72	2.77	2.66	.009	0.23
s Psychiatric syndromes	6.12	3.29			
GSRS Abdominal bloating					
No psychiatric syndromes	7.96	4.25	2.25	.026	0.20
Psychiatric syndromes	9.71	4.39			
GSRS Fullness					
No psychiatric syndromes	3.75	2.70	2.45	.015	0.22
Psychiatric syndromes	4.98	2.96			
PSS					
No psychiatric syndromes	21.99	7.39	5.22	.000	0.45
Psychiatric syndromes	29.32	8.72			
PHQ					
No psychiatric syndromes	5.72	3.14	2.90	.005	0.29
Psychiatric syndromes	8.07	4.85			
HADS Anxiety					
No psychiatric syndromes	5.17	3.02	6.63	.000	0.69
Psychiatric syndromes	10.78	5.12			
HADS Depression					
No psychiatric syndromes	6.99	3.28	3.08	.003	0.30
Psychiatric syndromes	9.41	4.66			
HADS Total score					
No psychiatric syndromes	12.17	5.38	5.60	.000	0.57
Psychiatric syndromes	20.24	8.68			
TAS-20 Total score					
No psychiatric syndromes	42.82	12.63	3.90	.000	0.36
Psychiatric syndromes	51.63	12.05			
TAS-20 DIF					
No psychiatric syndromes	12.95	5.49	5.31	.000	0.46
Psychiatric syndromes	18.46	6.38			
TAS-20 DDF					
No psychiatric syndromes	11.12	5.23	2.99	.003	0.28
Psychiatric syndromes	13.88	4.71			
IBDQ Systemic symptoms					
No psychiatric syndromes	24.13	6.45	5.03	.000	0.46
Psychiatric syndromes	18.27	6.37			
IBDQ Emotional health					
No psychiatric syndromes	61.73	11.68	5.49	.000	0.47
Psychiatric syndromes	49.37	14.47			
IBDQ Social function					
No psychiatric syndromes	27.31	8.05	2.64	.009	0.23
Psychiatric syndromes	23.39	8.68			

Comments:

The magnitude of the correlation coefficients of the clinical features of our sample shows that:

1) Overall quality of life was negatively affected stronger by symptoms (regardless of being psychologic or somatic) than inflammatory biomarkers. This result suggests that a comprehensive clinical evaluation of the patient's health status cannot be limited to standard medical assessment of biomarkers of inflammation;

2) The psychological variables were more strongly associated between them than with somatic symptoms. This result suggests that psychological factors and somatic symptoms largely but not completely overlapped;

3) Despite statistical differences, the association between variables and gender were in the small range of effect size, thus suggesting that gender differences are not relevant;

4) Age and psychological variables were not correlated;

5) Association between psychological variables and psychiatric condition of patients were in the medium range of effect size, specifically for depression and anxiety symptoms, perceived stress and quality of life.

Comparison between levels of disease activity at baseline

The comparison of IBD patients in quiescent and active stages of disease is shown in Table 16[4]. As expected, GSRS total score of patients with active disease was higher than quiescent patients (d=0.34), particularly in Pain (t = 4.28, $p < .001$), Abdominal bloating (t = 2.11, $p = .034$), and Diarrhea (t = 5.16, $p < .001$) subscales.

Also expectedly, IBDQ scores were higher in patients with remission (t = 2.42, $p = .018$), particularly in subscales of bowel symptoms (t = 4.56, $p < .001$), emotional health (t = 2.31, $p = .022$), and social function (t = 3.76, $p < .001$).

No significant differences were found between CD and UC patient.

[4] For readability purposes, Table 16 reports only scale scores showing significantly differences. The complete set of data is available upon request.

Table 16. *Comparison between patients in quiescent and active stages of disease at baseline*

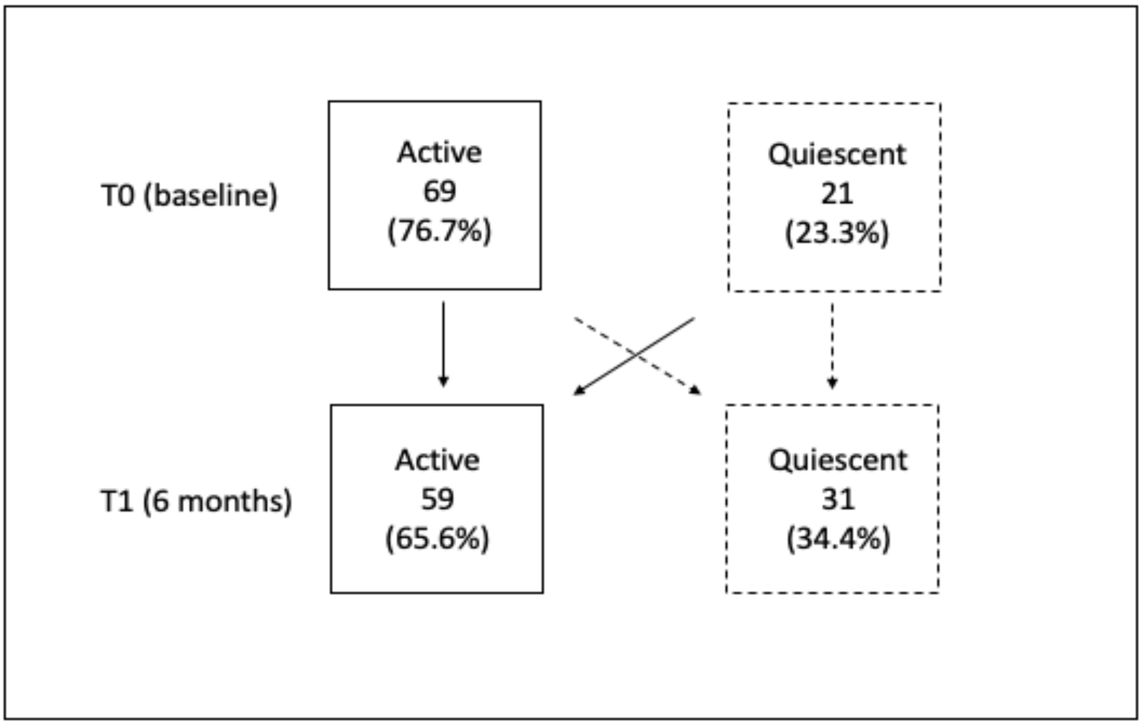
	Mean	DS	*t*	*p*	*d*
GSRS-IBS Total					
Quiescent	26.82	11.88	4.03	.000	0.34
Active	35.88	14.69			
GSRS-IBS Pain					
Quiescent	3.76	2.15	4.28	.000	0.35
Active	5.61	3.09			
GSRS-IBS Abdominal bloating					
Quiescent	7.24	3.92	2.11	.034	0.19
Active	8.85	4.46			
GSRS-IBS Diarrhea					
Quiescent	8.91	4.83	5.16	.000	0.43
Active	13.91	6.92			
IBDQ Total					
Quiescent	169.31	42.62	2.42	.018	0.23
Active	151.61	35.54			
IBDQ Bowel symptoms					
Quiescent	57.40	11.38	4.56	.000	0.4
Active	47.79	12.64			
IBDQ Emotional health					
Quiescent	62.47	13.77	2.31	.022	0.20
Active	57	13.27			
IBDQ Social function					
Quiescent	29.78	6.75	3.76	.000	0.12
Active	24.88	8.63			

Comparison between levels of disease activity at T1

At follow-up, 59 (65.6%) patients (31 men and 28 women) were still active or had a new flare-up of IBD symptoms at follow-up. Viceversa, 31 (34.4%) patients were still quiescent or their disease was in remission (Figure 4). Out of 90, 23 patients had a psychiatric syndrome according to MINI diagnostic interview and 14 of these had a relapse.

Figure 4 shows the cross-over paths of disease activity over time between quiescent and active IBD patients. At T1 (6 months follow-up) the active group included patients who were still active or had a flare up. Conversely, the quiescent group included patients who were still quiescent or became quiescent from being active at T0.

Figure 4. Disease Activity at baseline and at 6 months follow up.



As expected, compared to patients in the quiescent group, those in the active group at T1 reported higher scores on GSRS total scale (t = 2.14, p = .035) and on subscale 'Diarrhea' of GSRS (t = 3.85, $p < .001$).

Significant mean differences emerged for HADS total scores (t = 2.25, p = .023) at follow-up, particularly for the depression subscale (t=2.69, p = .009). These results indicate that patients who had a relapse after 6 months presented higher levels of anxiety and depression at follow up and higher levels of depression at baseline than patients in quiescent stage.

No differences between disease activity groups were found for PSS and PHQ.

As expected, higher IBDQ total scale score at follow up were found in remitted patients (d=0.38) than patients with active disease. Significant mean differences were found also for all four IBDQ subscales at follow up regarding bowel symptoms (t = 2.35, p = .000), emotional health (t = 2.98 , p = .004), systemic symptoms (t = 2.34, p = .022), and social function (t = 3.09, p = .003), with an higher effect size (d = .41) for "Bowel symptoms" subscale.

Comparison between levels of disease activity at 6 months follow up are presented in Table 17[5].

[5] For readability purposes, Table 17 reports only scale scores showing significantly differences. The complete set of data is available upon request.

Table 17. *Comparison between patients in quiescent stage and patients had a relapse at follow-up*

	Mean	DS	*t*	*p*	*d*
GSRS T1 Total score					
No relapse Relapse	27.42 33.47	11.27 13.43	2.14	.035	0.24
GSRS T1 Diarrhea					
No relapse Relapse	8.58 13.02	4.26 6.60	3.85	.000	0.41
HADS T1 Total score					
No relapse Relapse	10.84 14.75	6.81 7.97	2.25	.023	0.26
HADS T1 Depression					
No relapse Relapse	5.87 8.12	3.48 3.91	2.69	.009	0.30
IBDQ T1 Total score					
No relapse Relapse	179.00 153.37	26.67 41.53	3.55	.001	0.38
IBDQ T1 Bowel symptoms					
No relapse Relapse	58.16 49.36	7.13 14.13	3.89	.000	0.41
IBDQ T1 Emotional health					
No relapse Relapse	65.13 56.51	11.62 15.36	2.98	.004	0.32
IBDQ T1 Social function					
No relapse Relapse	31.00 26.31	5.12 9.29	3.09	.003	0.33

Compared with quiescent patients at 6 months, those in the active group reported also higher scores on subscale 'Diarrhea' of GSRS at baseline (t = 2.14, *p* = .035) and "Depression" at baseline (t = 2.44, *p* = .016) and lower scores on subscale "Bowel symptoms" of IBDQ (t = 2.35, *p* = .021). These results indicated that patients who were still active or relapsed after 6 months had higher levels of depression even at baseline than patients in quiescent stage (Table 18[6]).

Table 18. Comparison between baseline scores of patients in remission with patients had a flare up after 6 months

	Mean	DS	*t*	*p*	*d*
GSRS T0 Diarrhea					
No relapse	9.87	5.24	2.14	.035	0.25
Relapse	12.80	6.59			
HADS T0 Depression					
No relapse	5.77	3.13	2.44	.016	0.28
Relapse	7.63	3.55			
IBDQ T0 Bowel symptoms					
No relapse	55.58	8.89	2.35	.021	0.28
Relapse	49.66	12.47			

[6] For readability purposes, Table 18 reports only scale scores showing significantly differences. The complete set of data is available upon request.

Comments

1) At baseline, patients in active stage of disease showed not only more severe gastrointestinal symptoms than remitted patients, but also poorer QoL, especially regarding social functioning and emotional health, thus suggesting biomedical and psychological aspects were closely linked together;

2) As expected, no significant differences were found between CD and UC patients;

3) At follow-up, 59 (65.6%) patients (31 men and 28 women) were still active or had a new relapse of disease, while 31 (34.4%) patients were still in remission or had a clinically significant improvement;

4) Patients in the active disease group after 6 months reported higher levels of psychological distress (anxiety and depression) both at baseline and at follow-up and worse QoL than patients in remission.

5-HT-related and BDNF allelic variation in association with depressive symptoms

Table 19. Descriptive statistics of Genotyping Analysis

Genotypes *BDNF*			
Subjects N = 140 (87.5)	G/G 72 (51.4)	G/A 58 (41.4)	A/A 10 (7.1)
Genotypes *HTR2A*			
Subjects N = 140 (87.5)	G/G 29 (20.7)	G/A 87 (62.1)	A/A 24 (17.1)
Genotypes TPH2			
Subjects N = 140 (87.5)	G/G 70 (50)	G/T 62 (44.3)	T/T 8 (5.7)

The genotype and allele frequencies observed in our study sample are shown in Table 19. Cross-tabs' analyses were performed to assess possible associations between different gene polymorphisms and depression (Table 19). Allelic variations of BDNF and TPH2 polymorphisms were in accordance with the Hardy-Weinberg equilibrium (χ^2=0.13, p=.71 TPH2: χ^2=1.45, p=.22, respectively). Unlikely, HTR2A were not in equilibrium showing the homozygote reference and variant groups were underrepresented and the heterozygote group overrepresented (χ^2=0.8.35, p<.001).

Table 20. Association of Genotypes and Cases with clinically relevant Depression according to HADS

		BDNF Genotypes[a]		
	G/G	G/A	A/A	Total
HADS < 8	35 (46.7)	33 (44.0)	7 (9.3)	75
HADS ≥ 8	37 (56.9)	25 (38.5)	3 (4.6)	65
Total	72 (51.5)	58 (41.4)	10 (7.1)	140
		HTR2A Genotypes[b]		
	G/G	G/A	A/A	Total
HADS < 8	17 (22.7)	44 (58.7)	14 (18.6)	75
HADS ≥ 8	12 (18.5)	43 (66.1)	10 (15.4)	65
Total	29 (20.7)	87 (62.1)	24 (17.2)	140
		TPH2 Genotypes[c]		
	G/G	G/T	T/T	Total
HADS < 8	43 (57.3)	30 (40.0)	2 (2.7)	75
HADS ≥ 8	27 (41.5)	32 (49.2)	6 (9.3)	65
Total	70 (50.0)	64 (45.7)	6 (4.3)	140

[a] $\chi^2_{(2)} = 4.05$, $p = .13$

[b] $\chi^2_{(2)} = .830$, $p = .66$

[c] $\chi^2_{(2)} = 5.03$, $p = .08$

The results showed that no statistically differences in the distribution of studied genotypes were found in our sample (Table 20). Even though these genetic variants have been associated with depression-related outcomes (Illi et al., 2009; Martinowich et al., 2007; Tzvetkov et al., 2008), other recently studies failed to find such association (Border et al., 2019; Cozzolongo et al., 2015; Serretti et al., 2011).

Furthermore, the small sample size in single cells may hide significant results for insufficient power of the study. In fact, for example, patients carrying double-G allele were less likely to show depressive symptoms than those carrying at least one T allele (Fisher's exact test: p=.04), and patients carrying TPH2 double T alleles were only 8 (<10% of the whole sample) thus enhancing the risk of Type II error.

IBS-like symptoms in patients with and without endoscopic disease activity

Out of 160 patients, 72 (44.4%) were classified in the quiescent or mild activity after intestinal endoscopy, of whom 39 (54.2%) presented IBS-like symptoms according to the ROME III criteria (Table 21[7]). Intestinal endoscopy was performed at baseline and is used for the medical management of IBD patients at a regular basis at least once in a year. Differently from the clinical indices of disease activity that are based on symptoms, the endoscopic evaluation of the disease activity is based on the visual and/or bioptical assessment of the intestinal mucosa. Not always the two methods give identical results: patients may report active clinical symptoms even when there is no sign of mucosa inflammation, and vice versa.

Patients with IBS-like symptoms in quiescent or mild IBD had significantly more perceived stress and anxiety than non-IBS patients in quiescent IBD, scoring significantly higher on PSS scale ($t = 2.89$, $p = .005$), and HADS anxiety subscale ($t = 2.43$, $p = .018$). IBS-like in quiescent or mild IBD was significantly associated also with a poorer quality of life. IBS patients scored significantly lower on IBDQ total scale ($t = 3.17$, $p = .002$), and on all five subscales. Expectedly, significantly differences emerged also in GSRS total scale ($t = 12.52$, $p < .001$), and in all five subscales. Of note, most effect size coefficients were in the moderate (d between 0.50 and 0.80) to large (d>0.80) ranges, suggesting a strong association between subjectively perceived GI symptoms, psychological factors, and impaired quality of life.

No differences were found in inflammatory markers levels, suggesting that the subjectively perceived dimension of health status and related functional somatic symptoms are inter-related and more useful within a biopsychosocial framework of health care compared to the classic medical approach exclusively relying on biomarkers. This result suggests also that IBS-like symptoms in remitted IBD patients was not due to residual inflammation.

[7] For readability purposes, Table 21 reports only scale scores showing significantly differences. The complete set of data is available upon request.

__Table 21.__ Comparison between patients IBS-like and No IBS-like with endoscopically quiescent disease at baseline

	Mean	DS	*t*	*p*	*d*
GSRS-IBS Total score					
No IBS-like	17.55	3.23	12.52	.000	1.61
Yes IBS-like	39.26	10.24			
GSRS-IBS Pain					
No IBS-like	2.55	2.35	8.41	.000	0.64
Yes IBS-like	6.18	3.29			
GSRS-IBS Abdominal bloating					
No IBS-like	4.52	1.56	9.21	.000	1.15
Yes IBS-like	10.77	3.88			
GSRS-IBS Constipation					
No IBS-like	2.48	1.32	2.55	.014	0.28
Yes IBS-like	3.49	2.32			
GSRS-IBS Diarrhea					
No IBS-like	5.70	1.69	8.47	.000	1.11
Yes IBS-like	14.18	5.98			
GSRS-IBS Fullness					
No IBS-like	2.30	1.82	4.85	.000	0.50
Yes IBS-like	4.64	2.88			
PSS					
No IBS-like	19.42	7.98	2.89	.005	0.35
Yes IBS-like	25.51	9.59			
HADS Anxiety					
No IBS-like	4.64	3.54	2.43	.018	0.30
Yes IBS-like	7.13	4.90			
IBDQ Total score					
No IBS-like	178.85	39.11	3.17	.002	0.37
Yes IBS-like	152.46	31.53			
IBDQ Bowel symptoms					
No IBS-like	61.91	7.36	7.14	.000	0.87
Yes IBS-like	46.97	9.91			
IBDQ Systemic symptoms					
No IBS-like	25.42	7.17	2.29	.025	0.27
Yes IBS-like	21.72	6.53			
IBDQ Emotional health					
No IBS-like	66.45	9.82	3.05	.003	0.36
Yes IBS-like	58.54	12.15			
IBDQ Social function					
No IBS-like	31.21	4.96	4.01	.000	0.56
Yes IBS-like	25.23	7.59			

Comments

1) Using the Rome IV criteria, irritable bowel syndrome-like symptoms were found in half of IBD patients with endoscopically inactive disease. These patients who reported poor health even though no biomedical indices indicate they were ill are often labelled as "difficult patients" and generally physicians find very difficult their clinical management.
2) No differences were found in inflammatory markers levels, strengthening the associations with the subjectively perceived dimension of health status compared to biomarkers.
3) The presence of irritable bowel syndrome-like symptoms impaired the QoL of these patients, especially in the subscales of social functioning and bowel symptoms of IBDQ.
4) Patients with irritable bowel syndrome-like symptoms reported high levels of perceived stress and anxiety.

Psychological factors predicting clinical outcomes and QoL

A series of logistic and linear regression analyses were performed to analyze the role of psychological factors in predicting the clinical outcome in IBD patients. In the logistic regression analysis, disease activity (quiescent *vs.* active stage) at follow up served as the dependent (criterion) variable and baseline GSRS, HADS-Depression, HADS-Anxiety, and PSS scores served as independent (predictor) variables. As shown in Table 22, the HADS depression subscale proved to be the unique and strongest predictor (OR = 1.26, 95% CI = 1.06 – 1.51, p = 0.011) of disease activity.

A hierarchical linear regression analysis was performed to evaluate the role of psychological factors in predicting the severity of gastrointestinal symptoms in patients affected by IBD.

For the hierarchical linear regression, we used stepwise method. GSRS total scores at follow up served as the dependent (criterion) variable, while baseline and follow up HADS, PHQ, PSS, IBDQ scores served as the independent (predictor) variables. The model excluded HADS, PHQ, PSS baseline scores, and PSS follow-up scores. Step 1 including only HADS scores at follow-up produced a statistically significant fit (R^2 =.15, p < .001) accurately explaining 15% of the variance. The addition of PHQ scores at follow up in Step 2 increased the overall fit (R^2 =.22, p < .01) by adding 7% of explained variance. In the third step, adding IBDQ scores increased significantly the Cox and Snell R^2 from .15 to .54. The overall fit of the final model (R^2 =.54, p < .001) was significant, showing that IBDQ scores at follow-up represent the strongest independent predictor (t = 7.65) of gastrointestinal symptoms severity in IBD patients and accurately predicting 54% of the total variance.

Table 22. Results from logistic regression predicting disease activity

Facet/Domain	R^2	X^2	p	Final model						
				df	**B**	**SE**	**Wald**	***p***	**OR**	**95% C.I.**
GSRS	.02	2.1	.147	1	.04	.03	1.93	.165	1.04	0.99 -1.09
HADS Anxiety	.03	2.27	.321	1	-.04	.08	.19	.665	.97	0.82 – 1.13
HADS Depression	.09	8.61	.035	1	.23	.09	**6.54**	**.011**	**1.26**	1.06 – 1.51
PSS	.12	11.56	.021	1	-.06	.04	2.70	.101	.94	0.87 – 1.01
IBDQ	.12	11.88	.037	1	.01	.01	.31	.577	1.01	0.99 – 1.02

R^2= Cox & Snell R^2

Table 23. Hierarchical linear regression predicting gastrointestinal symptoms severity at follow-up

Step	Facet/Domain	R^2	R^2adj	R^2chg	F-chg	df	p	Final model			
								β	**SE**	***t***	***p***
Step 1	Block	.15	.14				.000				
	HADS T1							.64	.16	3.91	.000
Step 2		.22	.20	.07	8.26	1	.005				
	HADS T1							.31	.20	1.55	.125
	PHQ T1							1.23	.43	2.87	.000
Step 3		.54	.52	.32	58.46	1	.000				
	HADS T1							-.13	.16	.81	.422
	PHQ T1							.43	.35	1.22	.225
	IBDQ T1							-.24	.03	-7.65	.000

R^2= Cox & Snell R^2
Excluded variables (stepwise method): HADS T0; PHQ T0; PSS T0; PSS T1.

In addition, a hierarchical stepwise linear regression analysis evaluated the role of combined psychological factors and severity of gastrointestinal symptoms in predicting quality of life. IBDQ total scores at follow up served as the dependent (criterion) variable, while baseline and follow up PSS, GSRS, HADS- Depression, HADS-Anxiety, and PHQ scores served as the independent (predictor) variables. The model excluded PSS, HADS Depression, HADS Anxiety, PHQ baseline scores, and HADS Anxiety and PHQ follow-up scores. Step 1 including only PSS scores at follow-up produced a statistically significant fit (R^2 =.31, p < .001) accurately explaining 30% of the variance. In Step 2, the addition of GSRS scores at follow up increased the overall fit of the model (R^2 =.65, p < .001) by adding 34% of explained variance. In Step 3, GSRS scores at baseline contributed to increase the Cox and Snell R^2 only from .65 to .67. In the final step, HADS Depression scores at follow up added 3% of variance (t = 3.06, p < .001). The overall fit of the final model (R^2 =.70, p < .01) was significant, showing that

GSRS at follow-up represents the strongest predictor (t = 5.06) of quality of life in IBD patients followed by HADS Depression symptoms (t = 3.06), GSRS scores at baseline (t = 3.00) and perceived stress (t = 2.01).

Table 24. Hierarchical linear regression predicting quality of life at follow-up

Step	Facet/Domain	R^2	R^2adj	R^2chg	F-chg	df	p	Final model			
								β	SE	*t*	*p*
Step 1	Block	.31	.30				.000				
	PSS T1							-2.59	.41	-6.24	.000
Step 2		.65	.64	.34	82.79	1	.000				
	PSS T1							-1.68	.31	-3.34	.000
	GSRS T1							-1.83	.20	-9.10	.000
Step 3		.67	.66	.2	6.65	1	.012				
	PSS T1							-1.37	.33	-4.19	.000
	GSRS T1							-1.41	.26	-5.49	.000
	GSRS T0							- .70	.27	-2.58	.012
Step 4		.70	.69	.03	9.38	1	.003				
	PSS T1							- .75	.37	-2.01	.048
	GSRS T1							-1.26	.25	-5.06	.000
	GSRS T0							- .78	.26	-3.00	.004
	HADS Depression T1							-2.28	.75	-3.06	.003

R^2= Cox & Snell R^2
Excluded variables (stepwise method): PSS T0, HADS Depression T0, HADS Anxiety T0 and T1, PHQ T0 and T1.

Comments

1) The subscale “Depression” of HADS at baseline proved to be the unique and strongest predictor (OR = 1.26, 95% CI = 1.06 – 1.51, p = 0.011) of IBD active symptoms at the 6-month follow-up, suggesting that patients with depression at baseline had a higher risk to relapse.

2) Quality of life was found to be the strongest independent predictor of gastrointestinal symptoms severity in IBD patients.

3) The severity of gastrointestinal symptoms at follow up represents the strongest predictor of QoL in IBD patients followed by HADS Depressive symptoms, GSRS scores at baseline, and perceived stress.

3.6 Discussion

The main points of strength of the current research study are the design of the study (longitudinal with a 6 months of follow-up) and the assessment both of psychological factors and biological measures such as CRP, ESR, and Calprotectin. In addition, genotyping analyses were carried out for evaluating the role of genetic vulnerability (gene polymorphisms) in IBD patients reporting depressive symptoms.

In the present study, 72 IBD patients (44.4% of the sample) were in deep remission (absence of or mild endoscopic activity), as determined by colonoscopy with biopsies. Of these 72 patients, 39 (54.4%) met Roma IV criteria for IBS, suggesting persistent gastrointestinal problems, such as diarrhea and pain. Compared to IBD patients in deep remission without IBS-like symptoms, those having IBS like-symptoms reported significantly higher anxiety and psychological distress. Concerning biomarkers, as expected, no differences were found in levels of inflammatory markers between IBD patients with IBS like-symptoms and those without such symptoms. This finding is similar to that reported in a recent study by Perera et al. (2019). They showed that IBD patients in the quiescent stage of disease had severe symptoms of anxiety and depression. These results suggest that remission in IBD patients should include the assessment of IBS like symptoms. The colonoscopy, which has been used as the gold standard to establish remission in IBD patients, represents an important indicator of real inflammatory status but alone is not sufficient to identify remitted patients with IBD. A clinical assessment, including the evaluation of IBD-like symptoms and psychological factors, is recommended to establish levels of recovery in these patients.

The present follow up study showed that such psychological factors, particularly depression, significantly predicted clinical outcomes (relapse) in IBD patients. In other terms, patients with IBD having symptoms of depression were at higher risk to relapse than those without depression. These findings are in line with previous studies demonstrating that depressive symptoms had a negative impact on the course of IBD (Mittermaier et al., 2004; North et al., 1991). Assessing depression in this medical setting may therefore support clinicians to early identify IBD patients at higher risk for relapse. This assessment procedure should include not only rating scales for the evaluation of psychiatric symptoms such as depression, but also instruments for the examination of the positive mental health of IBD patients. Similarly, the clinical process of assessment should include not only clinician-rated instruments, but also patient-reported scales for the evaluation of the subjective state of psychological well-being. In the current longitudinal study, it was clearly demonstrated that such a subjective state of QoL was the strongest predictor of the severity of gastrointestinal symptoms. As has been shown in the present study, QoL and gastrointestinal symptoms had a bidirectional relationship: impaired levels of QoL were found to be associated with more severe gastrointestinal symptoms and, at the same time, gastrointestinal symptoms significantly predicted diminished QoL. This finding is in line with previous studies (Casellas et al., 2001; Pizzi et al., 2006) showing that there was a clinically significant and bidirectional relationship between symptoms severity and levels of QoL. As to QoL, another interesting result was that levels of QoL were affected more by symptoms, including both somatic and psychological ones, than inflammatory markers. Such a finding implies that a comprehensive clinical assessment of QoL cannot be limited to standard medical evaluation of inflammation indices but should include the examination of psychological variables contributing to health outcomes in IBD patients.

3.7 Clinical implications

These results represent an encouraging preliminary step in the study of mental health in patients affected by IBD. The high prevalence of psychological distress (e.g. depression) and poor quality of life in IBD patients associated with negative clinical outcomes such as an increased risk of relapses and more severe gastrointestinal symptoms justifies future research regarding both the management of psychological symptoms and the improvement of psychological well-being.

Our data suggest that psychological assessment may be clinically useful in identifying IBD patients at risk for poor clinical outcomes. This information may be helpful in planning IBD treatments for patients who are newly diagnosed, especially if such psychological assessment can identify specific psychological risk factors. Therefore, research on this field may offer new insights that can enhance IBD management by combining medical treatment with psychological therapy.

3.8 Limitations

The results of the current study should be understood in the context of some limitations. First, the sample size at follow-up was relatively small since at this time the study recruitment is still open for achieving the sample size objective. Second, lack of control group including healthy subjects for comparison with IBD patients. Third, the methodology of the study was limited by a failure to control for abnormal eating behavior, alcohol use, coffee consumption, smoking, and adherence to treatment. Since these behaviors represent a risk factor for exacerbating gastrointestinal symptoms, they should be controlled for in future studies. Finally, the interval of 6 months between baseline and follow-up assessment was quite short and precludes generalizing to the prediction of treatment outcomes over longer periods. Future studies with longer follow-up periods are needed.

APPENDICES

a. *Anamnestic report*

SCHEDA RICERCA IBD

CODICE ID___________________

Cognome/Nome ____

DATA ________________	1.☐ T0 (baseline) 2.☐ T1 (6 mesi) 3.☐ T2 (12 mesi)	1.☐ UC 2.☐ CD 3.☐ Indeterminata

Età ________	**Esordio IBD** (in anni) ____________	
Genere 1.☐M 2.☐F 3.☐Altro	**Numero medio di riacutizzazioni** ________ ☐ annue ☐ ultimi _____ anni	
Stato Civile 1. ☐ Celibe/nubile 2. ☐ Convivente 3. ☐ Coniugato/a 4. ☐ Separato/a Divorziato/a 5. ☐ Vedovo/a 6. ☐ Single	**Attività di malattia (valutazione clinica)** 1.☐ quiescente 2.☐ lieve 3.☐ moderata 4.☐ severa MAYO-FULL ______________ CDAI ______________ **Manifestazioni extra-intestinali**____________________________________ ____ ____	
Istruzione _______ anni	**Terapia attuale** 1.☐steroidi sistemici 2.☐steroidi locali 3.☐Anti-TNF$_\alpha$ 4.☐Immunomodulatori 5.☐5ASA 6.☐Anti-Integrina 7.☐Antibiotici 8.☐Altro	
Occupazione 1. ☐ Dipendente 2. ☐ Disoccupato 3. ☐ Casalinga 4. ☐ Pensionato 5. ☐ Studente 6. ☐ Autonomo 7. ☐ Altro:_________________	**Attività endoscopica di malattia** ☐ Mayo ______ ☐ SES-CD ______ ultima colonscopia eseguita in data _____________	☐ Quiescente ☐ Lieve ☐ Moderata ☐ Severa

Diagnosi MINI ____ **Patologie psichiatriche diagnosticate** (ultimi 10 anni) ____ ____ **Farmaci psicotropi assunti** (ultimi 10 anni) ____ ____ **Psicoterapia** (ultimi 10 anni) ☐SI ☐NO Se SI, da ________________ a ________________	**Check rilevazioni effettuate** ☐ prelievo di sangue genetica ☐ valori flogistici VES _____________ PCR _____________ ☐ calprotectina fecale __________________ ☐ GSRS-IBS ☐ PSS ☐ PHQ-15 ☐ HADS ☐ IDBQ ☐ TAS-20

b. ***The Gastrointestinal Symptom Rating Scale-IBS (GSRS-IBS)***

GSRS - IBS

Durante la settimana scorsa:

		No	Fastidio minimo	Fastidio scarso	Fastidio moderato	Abbastanza fastidio	Fastidio grave	Fastidio gravissimo
01.	Ha avuto dolore alla pancia?	☐	☐	☐	☐	☐	☐	☐
02.	Ha avuto dolore o fastidi all'intestino che si sono poi attenuati andando in bagno?	☐	☐	☐	☐	☐	☐	☐
03.	Ha avuto gonfiore intestinale?	☐	☐	☐	☐	☐	☐	☐
04.	Ha sentito aria nella pancia?	☐	☐	☐	☐	☐	☐	☐
05.	Ha avuto stitichezza (problemi nello svuotare l'intestino)?	☐	☐	☐	☐	☐	☐	☐
06.	Ha avuto diarrea (è andato molte volte in bagno)?	☐	☐	☐	☐	☐	☐	☐
07.	Ha avuto feci poco formate o liquide?	☐	☐	☐	☐	☐	☐	☐
08.	Ha avuto feci dure?	☐	☐	☐	☐	☐	☐	☐
09.	Ha sentito l'urgenza di andare in bagno per svuotare l'intestino?	☐	☐	☐	☐	☐	☐	☐
10.	Ha avuto la sensazione di non essersi completamente svuotato dopo essere andato in bagno?	☐	☐	☐	☐	☐	☐	☐
11.	Ha avuto la sensazione di sentirsi già pieno appena dopo aver iniziato a mangiare?	☐	☐	☐	☐	☐	☐	☐
12.	Ha avuto la sensazione di sentirsi ancora pieno anche molto tempo dopo aver finito di mangiare?	☐	☐	☐	☐	☐	☐	☐
13.	Ha visto che la pancia si è gonfiata visibilmente?	☐	☐	☐	☐	☐	☐	☐

c. ***Patient Health Questionnaire – 12 (PHQ-12)***

Nelle ultime 4 settimane, quanto è stato disturbato da uno o più dei seguenti fastidi fisici?	**Per niente**	**Un po'**	**Molto**
1. Dolore alla schiena	☐	☐	☐
2. Dolore a braccia, gambe e giunture (ginocchia, bacino, ecc)	☐	☐	☐
3. Dolori mestruali o altri problemi fisici legati al periodo mestruale [solo donne]	☐	☐	☐
4. Dolore al torace	☐	☐	☐
5. Mal di testa	☐	☐	☐
6. Vertigini	☐	☐	☐
7. Svenimenti	☐	☐	☐
8. Palpitazioni al cuore	☐	☐	☐
9. Affanno	☐	☐	☐
10. Dolori o problemi fisici durante i rapporti sessuali	☐	☐	☐
11. Stanchezza o mancanza di energie	☐	☐	☐
12. Difficoltà a dormire	☐	☐	☐

d. ***Toronto Alexithymia Scale -20 (TAS-20)***

Qui troverà delle affermazioni su come le persone reagiscono alle situazioni e come vedono la vita in generale.
Per favore, legga *attentamente* le affermazioni e risponda **sinceramente a TUTTE le domande**.
Per rispondere, metta una **crocetta X** sulla casella su cui è d'accordo.

E' d'accordo?

		No	**Non molto**	**Né si nè no**	**Si, in parte**	**Si**
01.	Sono spesso confuso circa le emozioni che provo	☐	☐	☐	☐	☐
02.	Mi è difficile trovare le parole giuste per esprimere i miei sentimenti	☐	☐	☐	☐	☐
03.	Provo delle sensazioni fisiche che neanche i medici capiscono	☐	☐	☐	☐	☐
04.	Riesco facilmente a descrivere i miei sentimenti	☐	☐	☐	☐	☐
05.	Preferisco approfondire i problemi piuttosto che descriverli semplicemente	☐	☐	☐	☐	☐
06.	Quando sono sconvolto, non so se sono triste, spaventato o arrabbiato	☐	☐	☐	☐	☐
07.	Sono spesso disorientato dalle sensazioni che provo nel mio corpo	☐	☐	☐	☐	☐
08.	Preferisco lasciare che le cose seguano il loro corso piuttosto che capire perché sono andate in quel modo	☐	☐	☐	☐	☐
09.	Provo sentimenti che non riesco proprio a identificare	☐	☐	☐	☐	☐
10.	E' essenziale essere in contatto con le proprie emozioni	☐	☐	☐	☐	☐
11.	Mi è difficile descrivere ciò che provo per gli altri	☐	☐	☐	☐	☐
12.	Gli altri mi chiedono di parlare di più dei miei sentimenti	☐	☐	☐	☐	☐
13.	Non riesco a capire cosa stia accadendo dentro di me	☐	☐	☐	☐	☐
14.	Spesso non so perché mi arrabbio	☐	☐	☐	☐	☐
15.	Con le persone preferisco parlare delle cose di tutti i giorni piuttosto che delle loro emozioni	☐	☐	☐	☐	☐
16.	Preferisco vedere spettacoli leggeri piuttosto che spettacoli a sfondo psicologico	☐	☐	☐	☐	☐
17.	Mi è difficile rivelare i miei sentimenti più profondi anche agli amici più intimi	☐	☐	☐	☐	☐
18.	Posso sentirmi vicino a una persona, anche se stiamo in silenzio	☐	☐	☐	☐	☐
19.	Trovo che l'esame dei miei sentimenti mi serve a risolvere i miei problemi personali	☐	☐	☐	☐	☐
20.	Cercare significati nascosti in film o commedie distoglie dal piacere dello spettacolo	☐	☐	☐	☐	☐

e. ***Hospital Anxiety and Depression Scale (HADS)***

Nella lista che segue sono elencati problemi e disturbi che le persone spesso hanno. La legga attentamente e cerchi di ricordare quanto ne ha sofferto **nella scorsa settimana**. Risponda a tutte le domande mettendo una crocetta **X**, senza saltarne nessuna.

		No	**Non molto**	**Abbastanza**	**Si**
1.	Mi sono sentito teso o “esaurito”	☐	☐	☐	☐
2.	Ho trovato piacevoli le cose che di solito mi piacciono	☐	☐	☐	☐
3.	Ho provato un senso di paura, come se dovesse accadere qualcosa di terribile	☐	☐	☐	☐
4.	Sono riuscito riderci sù e prenderla “con filosofia”	☐	☐	☐	☐
5.	Ho avuto la testa piena di preoccupazioni	☐	☐	☐	☐
6.	Mi sono sentito di buon umore	☐	☐	☐	☐
7.	Mi sono sentito tranquillo e rilassato	☐	☐	☐	☐
8.	Mi sono sentito come se andassi a rilento	☐	☐	☐	☐
9.	Mi sono sentito spaventato, come una morsa allo stomaco	☐	☐	☐	☐
10.	Non me ne è importato molto di curarmi nell’aspetto fisico	☐	☐	☐	☐
11.	Mi sono sentito in continuo stato di agitazione, come se non riuscissi a star fermo	☐	☐	☐	☐
12.	Ho pensato con piacere alle cose che devono accadere	☐	☐	☐	☐
13.	Ho avuto improvvise sensazioni di panico	☐	☐	☐	☐
14.	Sono riuscito a gustarmi la lettura di un libro o di un giornale oppure a vedere un programma alla televisione	☐	☐	☐	☐

f. ***IBD Quality of Life Questionnaire (IBDQ)***

Per favore, legga attentamente le affermazioni e risponda sinceramente a tutte le domande, indicando come si è sentito nelle ultime due settimane.

1. Ha avvertito dei movimenti nell'intestino?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
2. Si è sentito stanco, debole e affaticato?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
3. Si è sentito insofferente, irritato o agitato?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
4. Non è stato in grado di andare a lavoro, o a scuola, o ha avuto difficoltà a fare i servizi a casa, a causa dei suoi problemi intestinali?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
5. Le sue feci sono state liquide?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
6. Ha sentito di avere meno energia e meno forza?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
7. Si è preoccupato di poter subire un intervento chirurgico per la sua malattia?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**
8. Ha dovuto rimandare o anche rinunciare a qualche impegno preso, a causa dei suoi problemi intestinali?	**☐ 1. Tutto il tempo ☐ 2. La maggior parte del tempo ☐ 3. Una buona parte del tempo ☐ 4. Alcune volte ☐ 5. Poche volte ☐ 6. Quasi mai ☐ 7. Mai**

9. Ha avuto crampi addominali?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
10. Si è sentito generalmente poco bene?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
11. E' successo che si è preoccupato di dover necessariamente trovare un bagno a portata di mano?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
12. Ha avuto difficoltà a svagarsi durante il tempo libero (ad esempio, fare sport, andare a trovare amici, ecc.), come avrebbe voluto fare, a causa dei suoi problemi intestinali?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
13. Ha avuto dolori addominali?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
14. Ha avuto difficoltà a dormire o si è svegliato durante la notte?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
15. Si è sentito depresso o scoraggiato?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
16. Ha dovuto rinunciare ad andare da qualche parte perché non c'era il bagno a portata di mano?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
17. Ha provato una sensazione fastidiosa di dover fare spesso aria?	**È stato** **☐ 1. un serio problema** **☐ 2. un grande problema** **☐ 3. un problema importante** **☐ 4. un problema non serio** **☐ 5. un piccolo problema** **☐ 6. quasi nessun problema** **☐ 7. nessun problema**

18. Ha avuto difficoltà a mantenere o raggiungere il peso che avrebbe desiderato?	**È stato** **☐ 1. un serio problema** **☐ 2. un grande problema** **☐ 3. un problema importante** **☐ 4. un problema non serio** **☐ 5. un piccolo problema** **☐ 6. quasi nessun problema** **☐ 7. nessun problema**
19. Molti pazienti con problemi intestinali si preoccupano spesso della loro malattia (per paura di avere un cancro, di non stare più bene, di una ricaduta della malattia). Nelle ultime due settimane, ha avuto queste paure anche lei?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
20. Ha provato una sensazione fastidiosa di avere la pancia gonfia d'aria?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
21. Si è sentito rilassato e tranquillo?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
22. Ha avuto sangue nelle feci?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
23. Si è sentito imbarazzato per qualcosa dovuto ai suoi problemi intestinali?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
24. Ha avuto lo stimolo fastidioso di andare in bagno ma senza evacuare?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
25. Si è sentito sul punto di piangere o ha pianto?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
26. È successo che si è sporcata la biancheria intima?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**

27. Si è arrabbiato a causa dei suoi problemi intestinali?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
28. Sono diminuiti i rapporti sessuali a causa dei suoi problemi intestinali?	**☐ 1.Nessuna attività sessuale** **☐ 2. Molte limitazioni** **☐ 3. Moderate limitazioni** **☐ 4. Alcune limitazioni** **☐ 5. Poche limitazioni** **☐ 6. Quasi nessuna limitazione** **☐ 7. Nessuna limitazione**
29. Ha avuto problemi di stomaco?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
30. Si è sentito irritabile?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
31. Ha avuto la sensazione che gli altri non la capiscono?	**☐ 1. Tutto il tempo** **☐ 2. La maggior parte del tempo** **☐ 3. Una buona parte del tempo** **☐ 4. Alcune volte** **☐ 5. Poche volte** **☐ 6. Quasi mai** **☐ 7. Mai**
32. Si è sentito contento e soddisfatto della sua vita nella maggior tempo delle ultime due settimane?	**☐ 1. Molto insoddisfatto** **☐ 2. Generalmente insoddisfatto** **☐ 3. In qualche modo insoddisfatto** **☐ 4. Generalmente soddisfatto** **☐ 5. Soddisfatto** **☐ 6. Molto soddisfatto** **☐ 7. Estremamente soddisfatto**

g. ***Perceived Stress Scale (PSS)***

Nel corso dell'ultimo mese …	**Mai**	**Quasi mai**	**A volte**	**Abbastanz a spesso**	**Molto spesso**
1. Si è sentito turbato per qualcosa che le è successo inaspettatamente?	☐	☐	☐	☐	☐
2. Ha avvertito la sensazione di non riuscire a tenere sotto controllo cose per lei importanti?	☐	☐	☐	☐	☐
3. Si è sentito nervoso e stressato?	☐	☐	☐	☐	☐
4. È riuscito ad affrontare adeguatamente seccature che comunque l'avevano irritata?	☐	☐	☐	☐	☐
5. È riuscito ad affrontare efficacemente situazioni importanti accadute nella sua vita?	☐	☐	☐	☐	☐
6. Si è sentito sicuro della sua capacità di affrontare i suoi problemi personali?	☐	☐	☐	☐	☐
7. Ha avuto la sensazione che le cose siano andate per il verso giusto?	☐	☐	☐	☐	☐
8. Ha avuto la sensazione di non riuscire a gestire tutto ciò che aveva da fare?	☐	☐	☐	☐	☐
9. È riuscito a tenere sotto controllo la sua irritabilità?	☐	☐	☐	☐	☐
10. Ha avuto la sensazione di sentirsi al massimo?	☐	☐	☐	☐	☐
11. Si è arrabbiato per cose accadute al di fuori del suo controllo?	☐	☐	☐	☐	☐
12. Si è ritrovato a pensare in continuazione a cose che doveva portare a termine?	☐	☐	☐	☐	☐
13. È stato in grado di mantenere il controllo del suo tempo?	☐	☐	☐	☐	☐
14. Ha sentito che le difficoltà si stavano accumulando così tanto da non riuscire più a gestirle?	☐	☐	☐	☐	☐

h. ***Consenso informato***

INFORMATIVA PER IL PAZIENTE SULLO STUDIO
MODULO CONSENSO INFORMATO

Titolo dello studio: Studio sui predittori genetici, immunologici e psicologici del rischio di riacutizzazione nelle Inflammatory Bowel Disease (IBD).
Codice, versione e data del protocollo: PSY_IBD_2, V1_31/10/2018.
Responsabile locale della sperimentazione: Prof. Matteo Neri

Gentile Signore/Signora,
oggi la ricerca scientifica sui fattori (genetici, immunologici, psicologici) che incidono sul decorso delle patologie croniche rappresenta una parte integrante delle attività di diagnosi e cura in medicina. Per svolgere approfonditi studi sulla natura di molte malattie è necessario il contributo dei pazienti, attraverso la somministrazione di interviste e questionari psicologico-clinici, oltre alla raccolta di campioni biologici umani da pazienti affetti da tali patologie medico-croniche, in questo caso il Morbo di Crohn e la Rettocolite Ulcerosa.
Gli scopi dello studio a cui le proponiamo di partecipare sono i seguenti:

1. Analizzare il ruolo dei fattori psicologici (quali stress, ansia, depressione) sui livelli della qualità della vita dei pazienti affetti da malattie infiammatorie croniche intestinali.
2. Comprendere l'influenza che alcuni fattori psicologici (quali stress, ansia, depressione) potrebbero esercitare nel predire il rischio di riacutizzazione di malattia.
3. Indagare, attraverso il prelievo di un campione di sangue periferico su cui verranno effettuate specifiche analisi genetiche, la presenza di eventuali polimorfismi della serotonina al fine di individuare una vulnerabilità genetica per la depressione e il suo ruolo nelle riacutizzazioni di malattia e sui sintomi depressivi ad esse associate.
4. Analizzare il rapporto fra indici endoscopici (attraverso colonscopia di routine) di remissione e stress percepito dal paziente in relazione al rischio di riacutizzazione di malattia.

Si tratta di uno studio che non prevede la somministrazione di farmaci, ma solo la compilazione di questionari auto-somministrati, di un'intervista clinica e della raccolta di un campione di sangue periferico che non saranno utilizzati a scopo diagnostico, ma unicamente a scopo di ricerca scientifica.
La raccolta di ogni campione consiste nel prelievo di una provetta di sangue periferico, per un totale di circa 3 ml. I campioni di sangue periferico, prelevati presso l'Unità Operativa di Endoscopia digestiva e Gastroenterologia (P.O. "SS Annunziata" di Chieti) o presso l'Unità Operativa di Fisiopatologia Digestiva (P.O. "Spirito Santo" di Pescara), verranno trasferiti presso il Laboratorio di Genetica Medica del Dipartimento di Scienze Psicologiche, della Salute e del Territorio dell'Università "G. d'Annunzio" di Chieti (responsabile Prof. Liborio Stuppia), dove verranno conservati per un tempo massimo di 5 anni e saranno eseguite specifiche indagini genetiche volte ad individuare la presenza di eventuali polimorfismi della serotonina al fine di individuare una eventuale vulnerabilità genetica allo sviluppo di sintomi depressivi.

Un test genetico è un esame del DNA, eseguito analizzando un semplice campione di sangue periferico, che ricerca la presenza di alcune varianti nei suoi geni responsabili del tuo stato di salute. Il test genetico non è funzionale a una diagnosi né a una prognosi della malattia. L'obiettivo è quello di individuare dei fattori di predisposizione.
Dalla partecipazione a questo studio non ne trarrà diretto beneficio né vi sarà alcun compenso a suo favore, ma potranno beneficiare dei risultati dello studio tutti i pazienti che in futuro si troveranno in una situazione clinica simile alla sua. D'altra parte non vi è nessun potenziale rischio dal momento che lo studio non comporta alcun dispendio di energie né di tempo e non prevede procedure invasive di alcun genere, ma unicamente la compilazione dei questionari, l'intervista psicologico-clinica e il prelievo del campione di sangue che avverranno nel giorno stabilito per la visita gastroenterologica.
Il suo eventuale rifiuto a fornire il consenso per l'analisi dei dati non influenzerà in alcun modo il prosieguo della sua terapia e il suo rapporto con il medico di riferimento.
L'eventuale arruolamento nel presente studio non comporta nessuna modifica rispetto alla normale pratica clinica, lasciando invariato il piano di trattamento.
Il protocollo dello studio che le è stato proposto è stato redatto in conformità alle Norme di Buona Pratica Clinica della Unione Europea e alla revisione corrente della Dichiarazione di Helsinki ed è stato approvato dal Comitato Etico riconosciuto dall'Autorità Sanitaria competente.
I dati raccolti saranno trattati in via strettamente confidenziale, come da modello informativo che le verrà consegnato separatamente.
Potrà in ogni caso chiedere ogni informazione complementare sullo studio al Medico responsabile e ai suoi collaboratori che saranno disponibili a rispondere prima, durante e dopo lo studio (Prof. Matteo Neri; Telefono: [redacted], Prof. Laurino Grossi; Telefono: [redacted]).
La sua partecipazione a questo studio osservazionale no-profit è completamente gratuita e non è prevista alcuna spesa a suo carico.

Dopo aver discusso e aver ottenuto risposta a tutte le mie domande, ACCETTO liberamente di partecipare alla ricerca descritta sopra e di dare il mio consenso all'analisi statistica anonimizzata dei miei dati personali.
Il mio consenso non esonera in alcun modo il medico e il promotore dello studio dalle loro responsabilità.

LETTO E APPROVATO Data …………………

Ricercatore	Paziente
Nome e Cognome	Nome e Cognome
____________________	____________________
Firma	Firma
____________________	____________________

ALLEGATO E2-9

E2. STUDIO OSSERVAZIONALE NON FARMACOLOGICO – NO PROFIT

Titolo dello Studio: **STUDIO SUI PREDITTORI GENETICI, IMMUNOLOGICI E PSICOLOGICI DEL RISCHIO DI RIACUTIZZAZIONE NELLE INFLAMMATORY BOWEL DISEASE (IBD)**

Codice, versione e data del protocollo del Promotore: **PSY_IBD_2; V1_31/10/2018.**

Numero EudraCT: **N.D.**

Responsabile locale della sperimentazione: **PROF. MATTEO NERI**

Informativa e consenso al trattamento di dati
(art. 13 del Regolamento UE 2016/679 - G.D.P.R.)

INFORMATIVA E MANIFESTAZIONE DEL CONSENSO AL TRATTAMENTO DEI DATI PERSONALI

Gentile Signore/a, ai sensi dell'art. 13 del Regolamento UE 2016/679, in relazione ai dati personali che La riguardano e che saranno oggetto del trattamento, La informo di quanto segue.

Titolare del trattamento e Responsabile della protezione dei dati personali e relative finalità.

Il Centro di sperimentazione dell'*Unità Operativa di Endoscopia digestiva e Gastroenterologia (P.O. "SS. Annunziata" di Chieti)* e dell'*Unità Operativa di Fisiopatologia Digestiva (P.O. "Spirito Santo" di Pescara)*, il Promotore *Prof. Lelli Chiesa Pierluigi* e il Responsabile dello studio *Prof. Matteo Neri,* che hanno commissionato lo studio che Le è stato descritto, ciascuno per gli ambiti di propria competenza e nel rispetto delle regole di buona pratica clinica e della normativa in materia di sperimentazioni cliniche, tratteranno i Suoi dati personali, in particolare quelli sanitari, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo e nei limiti delle finalità dello Studio ed altri dati relativi alla Sua origine, ai Suoi stili di vita e alla Sua vita sessuale *(ecc…)*, esclusivamente in funzione della realizzazione dello studio e a fini di farmacovigilanza.
A tal fine i dati indicati saranno raccolti dal Centro di sperimentazione e trasmessi al Promotore e al Responsabile dello studio, così come alle persone o strutture esterne che agiscono per loro conto, tra le quali il Laboratorio di Genetica Medica (Dipartimento di Scienze Psicologiche, della Salute e del Territorio), coordinato dal Prof. Liborio Stuppia e il Laboratorio di Psicologia Clinica (Dipartimento di Scienze Psicologiche, della Salute e del Territorio), coordinato dal Prof. Piero Porcelli.

Il trattamento dei dati personali relativi a data di nascita, sesso e status sociale è indispensabile allo svolgimento dello studio: il rifiuto di conferirli non Le consentirà di parteciparvi.

Profilazione e Diffusione dei dati

I dati da Lei forniti verranno trattati secondo i principi di liceità, correttezza e trasparenza.
I Suoi dati personali non sono soggetti ad alcun processo decisionale interamente automatizzato, ivi compresa la profilazione.

Natura dei dati

Il medico che La seguirà nello studio La identificherà con un codice: i dati che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno trasmessi all'Azienda, registrati, elaborati e conservati unitamente a tale codice, alla Sua data di nascita, al sesso.

Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

Modalità del trattamento.

I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Sua partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale dell'Azienda farmaceutica o delle società esterne che eseguono per conto della prima il monitoraggio e la verifica dello studio, il Comitato etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Sua documentazione clinica originale, con modalità tali da garantire la riservatezza della Sua identità.

Esercizio dei diritti.

Potrà esercitare i diritti di cui all'art. 7 del Codice (es. accedere al Registro delle attività di Trattamento ed ai Suoi dati personali per: integrarli, aggiornarli, rettificarli, cancellarli, limitarne il trattamento, opporsi al loro trattamento per legittimi interessi, ecc.) rivolgendosi direttamente al centro di sperimentazione *(Prof. Matteo Neri; recapito:* [redacted]*).*

Potrà richiedere ed ottenere i Suoi dati personali in un formato strutturato e leggibile da dispositivo automatico, anche al fine di comunicare tali dati ad un altro titolare del trattamento (c.d. diritto alla portabilità dei dati personali);

Il consenso prestato con la sottoscrizione del presente modulo è in ogni momento revocabile.

Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio: in tal caso, i campioni biologici a Lei correlati verranno distrutti. Non saranno inoltre raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca. Tra i Suoi diritti rientrano quelli di proporre reclamo ad un'autorità di controllo (Autorità Garante per la Protezione dei dati personali - www.garanteprivacy.it).

Consenso
Sottoscrivendo tale modulo acconsento al trattamento dei miei dati personali e al loro trasferimento al di fuori dell'Unione europea per gli scopi della ricerca nei limiti e con le modalità indicate nell'informativa fornitami con il presente documento.

Data ______________________

Nome e Cognome dell'interessato *(in stampatello)* ______________________

Firma dell'interessato (leggibile)___________

REFERENCES

- Adams S.F., & Bornermann, P. H. (2013). Ulcerative colitis. *American Family Physician,* 87(19): 699-705.
- Addolorato, G., Capristo, E., Stefanini, G. F., & Gasbarrini, G. (1997). Inflammatory bowel disease: a study of the association between anxiety and depression, physical morbidity, and nutritional status. *Scandinavian journal of gastroenterology*, *32*(10), 1013-1021.
- American Psychiatric Association: Diagnostic and Statistical Manual of Psychiatric Disease, 4th Edition (DSM–IV). Washington, DC, American Psychiatric Publishing, 1994.
- Ananthakrishnan, A. N., Khalili, H., Higuchi, L. M., Bao, Y., Korzenik, J. R., Giovannucci, E. L., ... & Chan, A. T. (2012). Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. *Gastroenterology*, *142*(3), 482-489. doi.org/10.1053/j.gastro.2011.11.040
- Andrews, H., Barczak, P., & Allan, R. N. (1987). Psychiatric illness in patients with inflammatory bowel disease. *Gut*, *28*(12), 1600-1604. doi.org/10.1136/gut.28.12.1600
- Arnold, I., (2011). John Hattie: visible learning: a synthesis of over 800 meta-analyses relating to achievement. Int. Rev. Educ. 57, 219–221. https://doi.org/10.1007/ s11159-011-9198-8.
- Auzoux, J., Boschetti, G., Anon, B., Aubourg, A., Caulet, M., Poisson, L., ... & Nancey, S. (2019). Usefulness of confocal laser endomicroscopy for predicting postoperative recurrence in patients with Crohn's disease: a pilot study. *Gastrointestinal endoscopy*. Doi: https://doi.org/10.1016/j.gie.2019.02.030.

- Aziz, I., Mumtaz, S., Bholah, H., Chowdhury, F. U., Sanders, D. S., & Ford, A. C. (2015). High prevalence of idiopathic bile acid diarrhea among patients with diarrhea-predominant irritable bowel syndrome based on Rome III criteria. *Clinical Gastroenterology and Hepatology*, *13*(9), 1650-1655. Doi:10.1016/j.cgh.2015.03.002
- Bączyk, G., Formanowicz, D., Gmerek, Ł., & Krokowicz, P. (2017). Health-related quality of life assessment among patients with inflammatory bowel diseases after surgery–review. *Przeglad gastroenterologiczny*, *12*(1), 6.
- Bagby, R. M., Parker, J. D., & Taylor, G. J. (1994). The twenty-item Toronto Alexithymia Scale—I. Item selection and cross-validation of the factor structure. *Journal of psychosomatic research*, *38*(1), 23-32. doi.org/10.1016/0022-3999(94)90005-1
- Bagby, R. M., Taylor, G. J., & Parker, J. D. (1994). The twenty-item Toronto Alexithymia Scale—II. Convergent, discriminant, and concurrent validity. *Journal of psychosomatic research*, *38*(1), 33-40. doi.org/10.1016/0022-3999(94)90006-X
- Barbara, G., Cremon, C., & Stanghellini, V. (2014). Inflammatory bowel disease and irritable bowel syndrome: similarities and differences. *Current opinion in gastroenterology*, *30*(4), 352-358.
- Barclay, A. R., Russell, R. K., Wilson, M. L., Gilmour, W. H., Satsangi, J., & Wilson, D. C. (2009). Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. *The Journal of pediatrics*, *155*(3), 421-426. doi.org/10.1016/j.jpeds.2009.03.017
- Barrett, J. C., Hansoul, S., Nicolae, D. L., Cho, J. H., Duerr, R. H., Rioux, J. D., ... & Bitton, A. (2008). Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nature genetics*, *40*(8), 955. doi: 10.1038/NG.175

- Baumgart, D. C., & Carding, S. R. (2007). Inflammatory bowel disease: cause and immunobiology. *The Lancet*, *369*(9573), 1627-1640. doi.org/10.1016/S0140-6736(07)60750-8
- Baumgart, D. C., & Sandborn, W. J. (2012). Crohn's disease. *The Lancet*, *380*(9853), 1590-1605. doi.org/10.1016/S0140-6736(12)60026-9
- Bech, P., Carrozzino, D., Austin, S. F., Møller, S. B., & Vassend, O. (2016). Measuring euthymia within the Neuroticism Scale from the NEO Personality Inventory: a Mokken analysis of the Norwegian general population study for scalability. *Journal of affective disorders*, *193*, 99-102.
- Becker, H. M., Grigat, D., Ghosh, S., Kaplan, G. G., Dieleman, L., Wine, E., ... & Barkema, H. W. (2015). Living with inflammatory bowel disease: a Crohn's and Colitis Canada survey. *Canadian Journal of Gastroenterology and Hepatology*, *29*(2), 77-84.
- Benitez, J. M., & Louis, E. (2014). Can we predict the high-risk patient?. *Digestive Diseases*, 32(4), 328-336.
- Bernklev, T., Jahnsen, J., Henriksen, M., Lygren, I., Aadland, E., Sauar, J., ... & Moum, B. (2006). Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. *Inflammatory bowel diseases*, *12*(5), 402-412.
- Bernstein, C. N., Wajda, A., Svenson, L. W., MacKenzie, A., Koehoorn, M., Jackson, M., ... & Blanchard, J. F. (2006). The epidemiology of inflammatory bowel disease in Canada: a population-based study. *The American journal of gastroenterology*, *101*(7), 1559. doi: 10.1111/j.1572-0241.2006.00603.x

- Best, W.R., Becktel, J.M., Singleton, J.W., Kern, F. Jr. (1976). Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*, 70 (3): 439–444.
- Bień, A., Rzońca, E., Kańczugowska, A., & Iwanowicz-Palus, G. (2016). Factors affecting the quality of life and the illness acceptance of pregnant women with diabetes. *International journal of environmental research and public health*, *13*(1), 68.
- Bitton, A., Sewitch, M. J., Peppercorn, M. A., Edwardes, M. D. D., Shah, S., Ransil, B., & Locke, S. E. (2003). Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *The American journal of gastroenterology*, *98*(10), 2203-2208.
- Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *Journal of psychosomatic research*, *52*(2), 69-77. doi.org/10.1016/S0022-3999(01)00296-3
- Bjornsson, A. S., Bidwell, L. C., Brosse, A. L., Carey, G., Hauser, M., Mackiewicz Seghete, K. L., ... & Craighead, W. E. (2011). Cognitive–behavioral group therapy versus group psychotherapy for social anxiety disorder among college students: A randomized controlled trial. *Depression and Anxiety*, *28*(11), 1034-1042.
- Border, R., Johnson, E. C., Evans, L. M., Smolen, A., Berley, N., Sullivan, P. F., & Keller, M. C. (2019). No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *American Journal of Psychiatry*, *176*(5), 376-387.
- Boye, B., Jahnsen, J., Mokleby, K., Leganger, S., Jantschek, G., Jantschek, I., ... & Blomhoff, S. (2008). The INSPIRE study: are different personality traits related to disease-specific quality of life (IBDQ) in distressed patients with ulcerative colitis and Crohn's disease?. *Inflammatory bowel diseases*, *14*(5), 680-686.

- Bradesi, S., McRoberts, J. A., Anton, P. A., & Mayer, E. A. (2003). Inflammatory bowel disease and irritable bowel syndrome: separate or unified?. *Current opinion in gastroenterology*, *19*(4), 336-342.
- Bressi, C., Taylor, G., Parker, J., Bressi, S., Brambilla, V., Aguglia, E., ... & Todarello, O. (1996). Cross validation of the factor structure of the 20-item Toronto Alexithymia Scale: an Italian multicenter study. *Journal of psychosomatic research*, *41*(6), 551-559.
- Burisch, J., Jess, T., Martinato, M., & Lakatos, P. L. (2013). The burden of inflammatory bowel disease in Europe. *Journal of Crohn's and Colitis,* 7(4), 322–337. doi:10.1016/j.crohns.2013.01.010.
- Cámara, R. J., Ziegler, R., Begré, S., Schoepfer, A. M., & Von Känel, R. (2009). The role of psychological stress in inflammatory bowel disease: quality assessment of methods of 18 prospective studies and suggestions for future research. *Digestion*, 80(2), 129-139.
- Canavan, C., Abrams, K. R., & Mayberry, J. (2006). Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Alimentary pharmacology & therapeutics, 23(8), 1097-1104. doi.org/10.1111/j.1365-2036.2006.02854.x
- Castelnuovo, G. (2010). No medicine without psychology: the key role of psychological contribution in clinical settings. *Frontiers in psychology*, 1, 4-4.
- Carrozzino, D., & Porcelli, P. (2018). Alexithymia in gastroenterology and hepatology: a systematic review. *Frontiers in psychology*, *9*, 470.
- Carrozzino, D., Morberg, B. M., Siri, C., Pezzoli, G., & Bech, P. (2018). Evaluating psychiatric symptoms in Parkinson's Disease by a clinimetric analysis of the Hopkins Symptom Checklist (SCL-90-R). *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *81*, 131-137.

- Casellas, F., López-Vivancos, J., Badia, X., Vilaseca, J., & Malagelada, J. R. (2001). Influence of inflammatory bowel disease on different dimensions of quality of life. *European journal of gastroenterology & hepatology*, *13*(5), 567-572.
- Castelnuovo, G., Mauri, G., Simpson, S., Colantonio, A., & Goss, S. (2015). New technologies for the management and rehabilitation of chronic diseases and conditions. *BioMed research international*, 2015.
- Ciccocioppo, R., Klersy, C., Russo, M. L., Valli, M., Boccaccio, V., Imbesi, V., ... & Corazza, G. R. (2011). Validation of the Italian translation of the inflammatory bowel disease questionnaire. *Digestive and Liver Disease*, *43*(7), 535-541. doi.org/10.1016/j.dld.2010.12.014
- Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences. Lawrence Erlbaum, Hillsdale.
- Cohen, S., Kamarck, T., Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behaviour,* 24: 385-396
- Cohen, S., Kessler, R. C., & Gordon, L. U. (Eds.). (1997). *Measuring stress: A guide for health and social scientists*. Oxford University Press on Demand.
- Conley, S., Proctor, D. D., Jeon, S., Sandler, R. S., & Redeker, N. S. (2017). Symptom clusters in adults with inflammatory bowel disease. *Research in nursing & health*, *40*(5), 424-434. doi.org/10.1002/nur.21813
- Cooke, J., Zhang, H., Greger, L., Silva, A. L., Massey, D., Dawson, C., ... & Parkes, M. (2012). Mucosal genome-wide methylation changes in inflammatory bowel disease. *Inflammatory bowel diseases*, *18*(11), 2128-2137. doi.org/10.1002/ibd.22942
- Cornish, J. A., Tan, E., Simillis, C., Clark, S. K., Teare, J., & Tekkis, P. P. (2008). The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-

analysis. *The American journal of gastroenterology*, *103*(9), 2394. doi:10.1111/j.1572-0241.2008.02064.x

- Costa, P. T., & McCrae, R. R. (1992). *NEO-FFI: Neo Five-Factor Inventory*. Psychological Assessment Resources.
- Cozzolongo, R., Porcelli, P., Cariola, F., Giannuzzi, V., Lanzilotta, E., Gentile, M., ... & Leandro, G. (2015). Serotonin gene polymorphisms and lifetime mood disorders in predicting interferon-induced depression in chronic hepatitis C. *Journal of affective disorders*, *183*, 90-97.
- Creed, F., Fernandes, L., Guthrie, E., Palmer, S., Ratcliffe, J., Read, N., ... & North of England IBS Research Group. (2003). The cost-effectiveness of psychotherapy and paroxetine for severe irritable bowel syndrome. *Gastroenterology*, *124*(2), 303-317.
- Crohn, B. B., Ginzburg, L., & Oppenheimer, G. D. (1932). Regional ileitis: a pathologic and clinical entity. *Journal of the American Medical Association*, *99*(16), 1323-1329.
- De Boer, A. G., Bennebroek, E., Stokkers, P. C., Bockting, C. L., Sanderman, R., Hommes, D. W., ... & Frings-Dresen, M. H. (2016). Employment status, difficulties at work and quality of life in inflammatory bowel disease patients. *European journal of gastroenterology & hepatology*, *28*(10), 1130-1136.
- De Ridder, D., Geenen, R., Kuijer, R., & van Middendorp, H. (2008). Psychological adjustment to chronic disease. *The Lancet*, 372(9634), 246-255.
- De Santis, M., & Selmi, C. (2012). The therapeutic potential of epigenetics in autoimmune diseases. *Clinical Reviews in Allergy & Immunology*, *42*(1), 92-101.
- DeFilippis, E. M., Longman, R., Harbus, M., Dannenberg, K., & Scherl, E. J. (2016). Crohn's Disease: Evolution, epigenetics, and the emerging role of microbiome-

targeted therapies. *Current gastroenterology reports*, *18*(3), 13. doi.org/10.1007/s11894-016-0487-z

- DeJean, D., Giacomini, M., Vanstone, M., & Brundisini, F. (2013). Patient experiences of depression and anxiety with chronic disease: a systematic review and qualitative meta-synthesis. *Ontario health technology assessment series*, *13*(16), 1.
- DeLeon, P. H., Hagglund, K. J., Ragusea, S. A., and Sammons, M. T. (2003). Expanding roles for psy- chologists in the Twenty-First Century. In Handbook of Psychology: Clinical Psychology, Vol. 8, G. Stricker and T. A. Widiger, eds (Hoboken, NJ, John Wiley & Sons), pp. 551–568.
- Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. Gastroenterology 2016; 150:1262–1279.
- Drossman, D. A., & Dumitrascu, D. L. (2006). Rome III: New standard for functional gastrointestinal disorders. *Journal of Gastrointestinal and Liver Diseases*, *15*(3), 237.
- Drossman, D. A., & Ringel, Y. (2004). Kirsner's Inflammatory Bowel Disease.
- Drossman, D. A., & Ringel, Y. (2004). Psychosocial factors in ulcerative colitis and Crohn's diseases. Kirsner's Inflammatory Bowel Disease.
- Elsenbruch, S., Langhorst, J., Popkirowa, K., Müller, T., Luedtke, R., Franken, U., ... & Schedlowski, M. (2005). Effects of mind-body therapy on quality of life and neuroendocrine and cellular immune functions in patients with ulcerative colitis. *Psychotherapy and Psychosomatics*, 74(5), 277-287.
- Fabbri, S., Fava, G. A., Sirri, L., & Wise, T. N. (2007). Development of a new assessment strategy in psychosomatic medicine: the diagnostic criteria for psychosomatic research. In *Psychological Factors Affecting Medical Conditions* (Vol. 28, pp. 1-20). Karger Publishers.

- Farmer, R. G., Easley, K. A., & Farmer, J. M. (1992). Quality of life assessment by patients with inflammatory bowel disease. *Cleveland Clinic Journal of Medicine*, *59*(1), 35-42.
- Faulk, C., & Dolinoy, D. C. (2011). Timing is everything: the when and how of environmentally induced changes in the epigenome of animals. *Epigenetics*, *6*(7), 791-797. doi.org/10.4161/epi.6.7.16209
- Fava, G. A. (1982). Neurotic symptoms and major depressive illness. *Psychopathology*, *15*(4), 231-238.
- Fava, G. A., Belaise, C., & Sonino, N. (2010). Psychosomatic medicine is a comprehensive field, not a synonym for consultation liaison psychiatry. *Current psychiatry reports*, *12*(3), 215-221.
- Fava, G. A., Sonino, N., & Wise, T. N. (Eds.). (2011). *The Psychosomatic Assessment*. Karger Medical and Scientific Publishers.
- Flett, G. L., & Hewitt, P. L. (2002). Perfectionism: Theory, research, and treatment. Washington, DC: American Psychological Association.
- Flett, G. L., Baricza, C., Gupta, A., Hewitt, P. L., & Endler, N. S. (2011). Perfectionism, psychosocial impact and coping with irritable bowel disease: A study of patients with Crohn's disease and ulcerative colitis. *Journal of Health Psychology*, *16*(4), 561-571.
- Fuller-Thomson, E., & Sulman, J. (2006). Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. *Inflammatory bowel diseases*, *12*(8), 697-707.
- Gajendran, M., Loganathan, P., Catinella, A. P., & Hashash, J. G. (2018). A comprehensive review and update on Crohn's disease. *Disease-a-Month*, *64*(2), 20-57. doi.org/10.1016/j.disamonth.2017.07.001

Gastroenterology, *152*(2), 327-339. doi.org/10.1053/j.gastro.2016.10.012

- Garcia-Vega, E., & Fernandez-Rodriguez, C. (2004). A stress management programme for Crohn's disease. *Behaviour research and therapy*, 42(4), 367-383.
- Gilat T., Hacohen D., Lilos P. et al. (1987). Childhood factors in ulcerative colitis and Crohn's disease: an international cooperative study. *Scandinavian Journal of Gastroenterology*; 22:1009 – 24 .
- Goldberg, L. R. (1993). The structure of phenotypic personality traits. *American psychologist*, *48*(1), 26.
- Goldstein-Leever, A., Bass, J. A., Goyal, A., & Maddux, M. H. (2019). Health-related quality of life predicts psychology referral in youth with inflammatory bowel disease. *Journal of pediatric nursing*, 47, 73-77.
- Gracie, D. J., Williams, C. J., Sood, R., Mumtaz, S., Bholah, M. H., Hamlin, P. J., & Ford, A. C. (2017). Negative effects on psychological health and quality of life of genuine irritable bowel syndrome–type symptoms in patients with inflammatory bowel disease. *Clinical Gastroenterology and Hepatology*, *15*(3), 376-384. /doi.org/10.1016/j.cgh.2016.05.012
- Gradel, K. O., Nielsen, H. L., Schønheyder, H. C., Ejlertsen, T., Kristensen, B., & Nielsen, H. (2009). Increased short-and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. *Gastroenterology*, *137*(2), 495-501. doi.org/10.1053/j.gastro.2009.04.001
- Graff, L. A., Walker, J. R., & Bernstein, C. N. (2009). Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflammatory bowel diseases*, *15*(7), 1105-1118.
- Hall, N. J., Rubin, G. P., Dougall, A., Hungin, A. P. S., & Neely, J. (2005). The fight for 'health-related normality': a qualitative study of the experiences of individuals

living with established inflammatory bowel disease (IBD). *Journal of health psychology*, *10*(3), 443-455.

- Han, C., Pae, C. U., Patkar, A. A., Masand, P. S., Kim, K. W., Joe, S. H., & Jung, I. K. (2009). Psychometric properties of the Patient Health Questionnaire–15 (PHQ–15) for measuring the somatic symptoms of psychiatric outpatients. *Psychosomatics*, *50*(6), 580-585. doi.org/10.1016/S0033-3182(09)70859-X
- Häsler, R., Feng, Z., Bäckdahl, L., Spehlmann, M. E., Franke, A., Teschendorff, A., ... & Beck, S. (2012). A functional methylome map of ulcerative colitis. *Genome research*, *22*(11), 2130-2137. doi/10.1101/gr.138347.112.
- Häuser, W., Janke, K. H., Klump, B., & Hinz, A. (2011). Anxiety and depression in patients with inflammatory bowel disease: comparisons with chronic liver disease patients and the general population. *Inflammatory bowel diseases*, *17*(2), 621-632. https://doi.org/10.1002/ibd.21346
- Hendryx, M. S., Haviland, M. G., & Shaw, D. G. (1991). Dimensions of alexithymia and their relationships to anxiety and depression. *Journal of personality assessment*, *56*(2), 227-237.
- Higuchi, L. M., Khalili, H., Chan, A. T., Richter, J. M., Bousvaros, A., & Fuchs, C. S. (2012). A prospective study of cigarette smoking and the risk of inflammatory bowel disease in women. *The American journal of gastroenterology*, *107*(9), 1399. doi: 10.1038/ajg.2012.196
- Hisamatsu, T., Inoue, N., Yajima, T., Izumiya, M., Ichikawa, H., & Hibi, T. (2007). Psychological aspects of inflammatory bowel disease. Journal of gastroenterology, 42(17), 34-40.

- Hou, J. K., Abraham, B., & El-Serag, H. (2011). Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *The American journal of gastroenterology*, *106*(4), 563. doi:10.1038/ajg.2011.44
- Hunt, M. G., Moshier, S., & Milonova, M. (2009). Brief cognitive-behavioral internet therapy for irritable bowel syndrome. *Behaviour research and therapy*, *47*(9), 797-802. d oi.org/10.1016/j.brat.2009.05.002
- Hyphantis, T. N., Tomenson, B., Bai, M., Tsianos, E., Mavreas, V., & Creed, F. (2010). Psychological distress, somatization, and defense mechanisms associated with quality of life in inflammatory bowel disease patients. *Digestive diseases and sciences*, *55*(3), 724-732.
- Iglesias-Rey, M., Barreiro-de Acosta, M., Caamaño-Isorna, F., Rodríguez, I. V., Ferreiro, R., Lindkvist, B., ... & Dominguez-Munoz, J. E. (2013). Psychological factors are associated with changes in the health-related quality of life in inflammatory bowel disease. *Inflammatory bowel diseases*, *20*(1), 92-102.
- Illi, A., Setälä-Soikkeli, E., Viikki, M., Poutanen, O., Huhtala, H., Mononen, N., ... & Kampman, O. (2009). 5-HTR1A, 5-HTR2A, 5-HTR6, TPH1 and TPH2 polymorphisms and major depression. *Neuroreport*, *20*(12), 1125-1128.
- Issa, J. P. J., Ahuja, N., Toyota, M., Bronner, M. P., & Brentnall, T. A. (2001). Accelerated age-related CpG island methylation in ulcerative colitis. *Cancer research*, *61*(9), 3573-3577.
- Janke, K. H., Klump, B., Gregor, M., Meisner, C., & Haeuser, W. (2005). Determinants of life satisfaction in inflammatory bowel disease. *Inflammatory bowel diseases*, *11*(3), 272-286.
- Jantschek, G., Zeitz, M., Pritsch, M., Wirsching, M., Kloer, H. U., Studt, H. H., ... & Keller, W. (1998). Effect of psychotherapy on the course of Crohn's disease: Results of

the German prospective multicenter psychotherapy treatment study on Crohn's disease. *Scandinavian journal of gastroenterology*, 33(12), 1289-1296.

- Jenke, A. C., & Zilbauer, M. (2012). Epigenetics in inflammatory bowel disease. *Current opinion in gastroenterology*, *28*(6), 577-584. doi: 10.1097/MOG.0b013e328357336b
- Jordan, C., Sin, J., Fear, N. T., & Chalder, T. (2016). A systematic review of the psychological correlates of adjustment outcomes in adults with inflammatory bowel disease. *Clinical Psychology Review*, *47*, 28-40.
- Kaplan, G. G. (2015). The global burden of IBD: from 2015 to 2025. *Nature Reviews Gastroenterology & Hepatology, 12(12), 720–727.* doi:10.1038/nrgastro.2015.150
- Kaplan, G. G., & Ng, S. C. (2017). Understanding and preventing the global increase of inflammatory bowel disease. *Gastroenterology*, *152*(2), 313-321. doi.org/10.1053/j.gastro.2016.10.020
- Kaplan, G. G., Hubbard, J., Korzenik, J., Sands, B. E., Panaccione, R., Ghosh, S., ... & Villeneuve, P. J. (2010). The inflammatory bowel diseases and ambient air pollution: a novel association. *The American journal of gastroenterology*, *105*(11), 2412.
- Kaplan, G. G., Jackson, T., Sands, B. E., Frisch, M., Andersson, R. E., & Korzenik, J. (2008). The risk of developing Crohn's disease after an appendectomy: a meta-analysis. *The American journal of gastroenterology*, *103*(11), 2925. Doi. 10.1111/j.1572-0241.2008.02118.x
- Kessler, R. C. (2007). The global burden of anxiety and mood disorders: putting ESEMeD findings into perspective. *The Journal of clinical psychiatry*, *68*(Suppl 2), 10.
- Khalili, H., Higuchi, L. M., Ananthakrishnan, A. N., Manson, J. E., Feskanich, D., Richter, J. M., ... & Chan, A. T. (2012). Hormone therapy increases risk of ulcerative

colitis but not Crohn's disease. *Gastroenterology*, *143*(5), 1199-1206. doi.org/10.1053/j.gastro.2012.07.096

- Kiecolt-Glaser, J. K., McGuire, L., Robles, T. F., & Glaser, R. (2002). Emotions, morbidity, and mortality: new perspectives from psychoneuroimmunology. *Annual review of psychology*, 53(1), 83-107.
- Kroenke, K. (2007). Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. *Psychosomatic medicine*, *69*(9), 881-888.
- Kroenke, K., Spitzer, R. L., & Williams, J. B. (2002). The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosomatic medicine*, *64*(2), 258-266.
- Kumar, N., Khunger, M., Gupta, A., and Garg, N. (2015). A content analysis of smartphone-based applications for hypertension management. *J. Am. Soc. Hypertens*. 2, 130–136. doi: 10.1016/j.jash.2014. 12.001
- Ku¨nsebeck HW, Lempa W, Freyberger H. Kurz- und Langzeiteffekte erga¨nzender Psychotherapie bei Morbus Crohn. In: Lamprecht F, ed. Spezialisierung und Integration in Psychosomatik und Psychotherapie. Berlin: Springer; 1987:253Y262.
- Kurina, L. M., Goldacre, M. J., Yeates, D., & Gill, L. E. (2001). Depression and anxiety in people with inflammatory bowel disease. *Journal of Epidemiology & Community Health*, *55*(10), 716-720.
- La Barbera, D., Bonanno, B., Rumeo, M. V., Alabastro, V., Frenda, M., Massihnia, E., ... & Tumminello, M. (2017). Alexithymia and personality traits of patients with inflammatory bowel disease. *Scientific reports*, *7*, 41786.
- Lahey, B. B. (2009). Public health significance of neuroticism. *American Psychologist*, *64*(4), 241.

- Langhorst, J., Hofstetter, A., Wolfe, F., & Häuser, W. (2013). Short-term stress, but not mucosal healing nor depression was predictive for the risk of relapse in patients with ulcerative colitis: a prospective 12-month follow-up study. *Inflammatory bowel diseases*, *19*(11), 2380-2386.
- Lazarus, R. S., & Folkman, S. (1984). *Stress, appraisal, and coping*. Springer publishing company.
- Lerebours, E., Gower-Rousseau, C., Merle, V., Brazier, F., Debeugny, S., Marti, R., ... & Cortot, A. (2007). Stressful life events as a risk factor for inflammatory bowel disease onset: a population-based case–control study. *The American journal of gastroenterology*, *102*(1), 122.
- Lima, F. D. A. V., da Rocha Ribeiro, T. C., Chebli, L. A., de Lima Pace, F. H., de Miranda Chaves, L. D., Ribeiro, M. S., & Chebli, J. M. F. (2012). Mood swings in patients with Crohn's disease: incidence and associated factors. *Revista da Associação Médica Brasileira (English Edition)*, *58*(4), 481-488.
- Lin, Z., Hegarty, J. P., Yu, W., Cappel, J. A., Chen, X., Faber, P. W., ... & Koltun, W. A. (2012). Identification of disease-associated DNA methylation in B cells from Crohn's disease and ulcerative colitis patients. *Digestive diseases and sciences*, *57*(12), 3145-3153.
- Lipowski, Z. J. (1986). Psychosomatic Medicine: Past and Present Part I. Historical Background. *The Canadian Journal of Psychiatry*, *31*(1), 2-7.
- Lipowski, Z. J. (1988). Somatization: the concept and its clinical application. *Am J Psychiatry*, *145*(11), 1358-1368.
- Liu, J. Z., van Sommeren, S., Huang, H., Ng, S. C., Alberts, R., Takahashi, A., ... & Abedian, S. (2015). Association analyses identify 38 susceptibility loci for

inflammatory bowel disease and highlight shared genetic risk across populations. *Nature genetics*, *47*(9), 979.

- Lix, L. M., Graff, L. A., Walker, J. R., Clara, I., Rawsthorne, P., Rogala, L., ... & Bernstein, C. N. (2008). Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. *Inflammatory bowel diseases*, *14*(11), 1575-1584.
- Loftus, E. V., Jr (2004). Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology,* 126 (6), 1504-1517. doi.org/10.1053/j.gastro.2004.01.063
- Lumley, M. A., Stettner, L., & Wehmer, F. (1996). How are alexithymia and physical illness linked? A review and critique of pathways. *Journal of psychosomatic research*, *41*(6), 505-518.
- Lutgens, M. W., Vleggaar, F. P., Schipper, M. E., Stokkers, P. C., van der Woude, C. J., Hommes, D. W., ... & Samsom, M. (2008). High frequency of early colorectal cancer in inflammatory bowel disease. *Gut*, *57*(9), 1246-1251. doi.org/10.1136/gut.2007.143453
- Malik, T. A. (2015). Inflammatory bowel disease: historical perspective, epidemiology, and risk factors. *Surgical Clinics*, *95*(6), 1105-1122. doi.org/10.1016/j.suc.2015.07.006
- Manzoni, G. M., Pagnini, F., Corti, S., Molinari, E., & Castelnuovo, G. (2011). Internet-based behavioral interventions for obesity: an updated systematic review. *Clinical practice and epidemiology in mental health*: CP & EMH, 7, 19.
- Mardini, H. E., Kip, K. E., & Wilson, J. W. (2004). Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. *Digestive diseases and sciences*, *49*(3), 492-497.

- Martinowich, K., Manji, H., & Lu, B. (2007). New insights into BDNF function in depression and anxiety. *Nature neuroscience*, *10*(9), 1089.
- Maunder, R. G., & Esplen, M. J. (2001). Supportive-expressive group psychotherapy for persons with inflammatory bowel disease. *The Canadian Journal of Psychiatry*, 46(7), 622-626.
- Maunder, R. G., & Levenstein, S. (2008). The role of stress in the development and clinical course of inflammatory bowel disease: epidemiological evidence. Current molecular medicine, 8(4), 247-252.
- Maunder, R. G., Lancee, W. J., Hunter, J. J., Greenberg, G. R., & Steinhart, H. A. (2005). Attachment insecurity moderates the relationship between disease activity and depressive symptoms in ulcerative colitis. *Inflammatory bowel diseases*, *11*(10), 919-926.
- Mawdsley, J. E., & Rampton, D. S. (2005). Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut*, *54*(10), 1481-1491.
- McGovern, D. P., Kugathasan, S., & Cho, J. H. (2015). Genetics of inflammatory bowel diseases. *Gastroenterology*, *149*(5), 1163-1176. doi.org/10.1053/j.gastro.2015.08.001
- Mikocka-Walus, A., Pittet, V., Rossel, J. B., von Känel, R., Anderegg, C., Bauerfeind, P., ... & Biedermann, L. (2016). Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clinical gastroenterology and hepatology*, *14*(6), 829-835. doi.org/10.1016/j.cgh.2015.12.045
- Mikocka-Walus, A., Pittet, V., Rossel, J. B., von Känel, R., Anderegg, C., Bauerfeind, P., ... & Biedermann, L. (2016). Symptoms of depression and anxiety are

independently associated with clinical recurrence of inflammatory bowel disease. *Clinical gastroenterology and hepatology*, *14*(6), 829-835.

- Mikocka-Walus, A. A., Turnbull, D. A., Moulding, N. T., Wilson, I. G., Andrews, J. M., & Holtmann, G. J. (2007). Controversies surrounding the comorbidity of depression and anxiety in inflammatory bowel disease patients: a literature review. *Inflammatory bowel diseases*, *13*(2), 225-234.
- Mitchell, A., Guyatt, G., Singer, J., Irvine, E. J., Goodacre, R., Tompkins, C., ... & Wagner, F. (1988). Quality of life in patients with inflammatory bowel disease. *Journal of clinical gastroenterology*, *10*(3), 306-310.
- Mittermaier, C., Dejaco, C., Waldhoer, T., Oefferlbauer-Ernst, A., Miehsler, W., Beier, M., ... & Moser, G. (2004). Impact of depressive mood on relapse in patients with inflammatory bowel disease: a prospective 18-month follow-up study. *Psychosomatic medicine*, *66*(1), 79-84.
- Molodecky, N. A., Soon, S., Rabi, D. M., Ghali, W. A., Ferris, M., Chernoff, G., ... & Kaplan, G. G. (2012). Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*, *142*(1), 46-54. doi.org/10.1053/j.gastro.2011.10.001
- Monteiro, S., Dias de Castro, F., Leite, S., Moreira, M. J., & Cotter, J. (2019). Low fecal calprotectin predicts clinical remission in Crohn's disease patients: the simple answer to a challenging question. Scandinavian journal of gastroenterology, 54(1), 49-54.
- Moradkhani, A., Beckman, L. J., & Tabibian, J. H. (2013). Health-related quality of life in inflammatory bowel disease: psychosocial, clinical, socioeconomic, and demographic predictors. Journal of Crohn's and Colitis, 7(6), 467-473.

- Moreno-Jiménez, B., Blanco, B. L., Rodríguez-Muñoz, A., & Hernández, E. G. (2007). The influence of personality factors on health-related quality of life of patients with inflammatory bowel disease. *Journal of psychosomatic research*, *62*(1), 39-46.
- Morgan, X. C., Tickle, T. L., Sokol, H., Gevers, D., Devaney, K. L., Ward, D. V., ... & Bousvaros, A. (2012). Dysfunction of the intestinal microbiome in inflammatory bowel disease and treatment. *Genome biology*, *13*(9), R79. doi.org/10.1186/gb-2012-13-9-r79
- Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *The Lancet*, *370*(9590), 851-858.
- Mowat, C., Cole, A., Windsor, A. L., Ahmad, T., Arnott, I., Driscoll, R., ... & Lees, C. (2011). Guidelines for the management of inflammatory bowel disease in adults. *Gut*, *60*(5), 571-607.
- Müller, H. M., Oberwalder, M., Fiegl, H., Morandell, M., Goebel, G., Zitt, M., ... & Widschwendter, M. (2004). Methylation changes in faecal DNA: a marker for colorectal cancer screening? *The Lancet*, *363*(9417), 1283-1285. doi.org/10.1016/S0140-6736(04)16002-9
- Mussell, M., Böcker, U., Nagel, N., Olbrich, R., & Singer, M. V. (2003). Reducing psychological distress in patients with inflammatory bowel disease by cognitive-behavioural treatment: exploratory study of effectiveness. *Scandinavian journal of gastroenterology*, 38(7), 755-762.
- Na, S. Y., & Moon, W. (2019). Perspectives on Current and Novel Treatments for Inflammatory Bowel Disease. *Gut and liver*. doi: 10.5009/gnl19019

- Nahon, S. (2011). W09-04-Socioeconomic and psychological factors associated with non-adherence to treatment in IBD patients: Results of the isseo survey. *European Psychiatry*, *26*, 2221.
- Nater, U. M., Jones, J. F., Lin, J. M. S., Maloney, E., Reeves, W. C., & Heim, C. (2010). Personality features and personality disorders in chronic fatigue syndrome: a population-based study. *Psychotherapy and psychosomatics*, *79*(5), 312-318.
- Ng, S. C., Shi, H. Y., Hamidi, N., Underwood, F. E., Tang, W., Benchimol, E. I., ... & Sung, J. J. (2017). Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet*, *390*(10114), 2769-2778. d oi.org/10.1016/S0140-6736(17)32448-0
- Niess, J. H., Mönnikes, H., Dignass, A. U., Klapp, B. F., & Arck, P. C. (2002). Review on the influence of stress on immune mediators, neuropeptides and hormones with relevance for inflammatory bowel disease. *Digestion*, *65*(3), 131-140.
- Nigro, G., Angelini, G., Grosso, S. B., Caula, G., & Sategna-Guidetti, C. (2001). Psychiatric predictors of noncompliance in inflammatory bowel disease: psychiatry and compliance. *Journal of clinical gastroenterology*, *32*(1), 66-68.
- Noël, P. H., Williams, J. W., Unützer, J., Worchel, J., Lee, S., Cornell, J., ... & Hunkeler, E. (2004). Depression and comorbid illness in elderly primary care patients: impact on multiple domains of health status and well-being. *The Annals of Family Medicine*, *2*(6), 555-562.
- North, C. S., Alpers, D. H., Helzer, J. E., Spitznagel, E. L., & Clouse, R. E. (1991). Do life events or depression exacerbate inflammatory bowel disease?: A prospective study. *Annals of internal Medicine*, *114*(5), 381-386.
- O' Conner J.F., Daniels G., Flood C., et al. (1964). An evaluation of the effectiveness of psychotherapy in the treatment of ulcerative colitis. *Ann Int Med.*, 60:587.

- Parker, J. D., Michael Bagby, R., Taylor, G. J., Endler, N. S., & Schmitz, P. (1993). Factorial validity of the 20-item Toronto Alexithymia Scale. *European Journal of personality*, *7*(4), 221-232. doi.org/10.1002/per.2410070403
- Peppercorn, M. A., & Cheifetz, A. S. (2019). Definitions, epidemiology, and risk factors for inflammatory bowel disease in adults. UpToDate, Basow, DS (Ed).
- Persoons, P., Vermeire, S., Demyttenaere, K., Fischler, B., Vandenberghe, J., Van Oudenhove, L., ... & Rutgeerts, P. (2005). The impact of major depressive disorder on the short-and long-term outcome of Crohn's disease treatment with infliximab. *Alimentary pharmacology & therapeutics*, *22*(2), 101-110.
- Petronis, A. (2010). Epigenetics as a unifying principle in the aetiology of complex traits and diseases. *Nature*, *465*(7299), 721.
- Pinninti, N. R., Madison, H., Musser, E., & Rissmiller, D. (2003). MINI International Neuropsychiatric Schedule: clinical utility and patient acceptance. European Psychiatry, 18(7), 361–364. doi:10.1016/j.eurpsy.2003.03.004
- Piovezani Ramos G., & Papadakis K.A. (2019). Mechanisms of Disease: Inflammatory Bowel Diseases. *Mayo Clinic Proceedings,* 94(1), 155-165. doi.org/10.1016/j.mayocp.2018.09.013
- Porcelli, P. (2009). *Medicina psicosomatica e psicologia clinica: modelli teorici, diagnosi, trattamento*. Cortina.
- Porcelli, P., Leoci, C., & Guerra, V. (1996). A prospective study of the relationship between disease activity and psychologic distress in patients with inflammatory bowel disease. *Scandinavian journal of gastroenterology*, *31*(8), 792-796.
- Porcelli, P., Leoci, C., Guerra, V., Taylor, G. J., & Bagby, R. M. (1996). A longitudinal study of alexithymia and psychological distress in inflammatory bowel

disease. *Journal of psychosomatic research*, *41*(6), 569-573. doi.org/10.1016/S0022-3999(96)00221-8

- Porcelli, P., Leoci, C., Guerra, V., Taylor, G. J., & Bagby, R. M. (1996). A longitudinal study of alexithymia and psychological distress in inflammatory bowel disease. *Journal of psychosomatic research*, *41*(6), 569-573.
- Porcelli, P., Taylor, G. J., Bagby, R. M., & De Carne, M. (1999). Alexithymia and functional gastrointestinal disorders. Psychotherapy and Psychosomatics, 68(5), 263-269.
- Porcelli, P., Tulipani, C., Maiello, E., Cilenti, G., & Todarello, O. (2007). Alexithymia, coping, and illness behavior correlates of pain experience in cancer patients. *Psycho-Oncology: Journal of the Psychological, Social and Behavioral Dimensions of Cancer*, *16*(7), 644-650.
- Porcelli, P., Zaka, S., Leoci, C., Centonze, S., & Taylor, G. J. (1995). Alexithymia in inflammatory bowel disease. *Psychotherapy and psychosomatics*, *64*(1), 49-53. doi.org/10.1159/000288990
- Porter, C. K., Tribble, D. R., Aliaga, P. A., Halvorson, H. A., & Riddle, M. S. (2008). Infectious gastroenteritis and risk of developing inflammatory bowel disease. *Gastroenterology*, *135*(3), 781-786. doi.org/10.1053/j.gastro.2008.05.081
- Price, A. B. (1978). Overlap in the spectrum of non-specific inflammatory bowel disease--'colitis indeterminate'. *Journal of clinical pathology*, *31*(6), 567-577. doi.org/10.1136/jcp.31.6.567
- Quetglas, E. G., Mujagic, Z., Wigge, S., Keszthelyi, D., Wachten, S., Masclee, A., & Reinisch, W. (2015). Update on pathogenesis and predictors of response of therapeutic strategies used in inflammatory bowel disease. World journal of gastroenterology, 21(44), 12519.

- Reddy, B. K., Delen, D., & Agrawal, R. K. (2018). Predicting and explaining inflammation in Crohn's disease patients using predictive analytics methods and electronic medical record data. Health informatics journal, doi: https://doi.org/10.1177/1460458217751015.
- Ricciuto, A., & Griffiths, A. M. (2019). Clinical value of fecal calprotectin. Critical reviews in clinical laboratory sciences, (just-accepted), 1-37.
- Riley, S. A., Mani, V., Goodman, M. J., & Lucas, S. (1990). Why do patients with ulcerative colitis relapse?. *Gut*, *31*(2), 179-183.
- Rocchi, A., Benchimol, E. I., Bernstein, C. N., Bitton, A., Feagan, B., Panaccione, R., ... & Ghosh, S. (2012). Inflammatory bowel disease: a Canadian burden of illness review. *Canadian Journal of Gastroenterology and Hepatology*, *26*(11), 811-817. doi.org/10.1155/2012/984575
- Ruini, C., Ottolini, F., Rafanelli, C., Tossani, E., Ryff, C. D., & Fava, G. A. (2003). The relationship of psychological well-being to distress and personality. *Psychotherapy and Psychosomatics*, *72*(5), 268-275.
- Rutgeerts P., Sandborn W.J., Feagan B.G., Reinisch W., et al. (2005). Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.*, 353 (23): 2462-2476.
- Ryff, C. D. (2014). Psychological well-being revisited: Advances in the science and practice of eudaimonia. *Psychotherapy and psychosomatics*, *83*(1), 10-28.
- Sajadinejad, M. S., Asgari, K., Molavi, H., Kalantari, M., & Adibi, P. (2012). Psychological issues in inflammatory bowel disease: an overview. *Gastroenterology research and practice*, *2012*.

- Salminen, S., Gibson, G. R., McCartney, A. L., & Isolauri, E. (2004). Influence of mode of delivery on gut microbiota composition in seven years old children. *Gut*, *53*(9), 1388-1389. doi.org/10.1136/gut.2004.041640
- Santoro, E., Castelnuovo, G., Zoppis, I., Mauri, G., & Sicurello, F. (2015). Social media and mobile applications in chronic disease prevention and management. *Frontiers in psychology*, 6, 567.
- Sartor, R. B., & Wu, G. D. (2017). Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches.
- Satsangi, J., Silverberg, M. S., Vermeire, S., & Colombel, J. (2006). The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*, *55*(6), 749-753. doi.org/10.1136/gut.2005.082909
- Schmidt, C., Marth, T., Wittig, B. M., & Hombach, A. (2002). Interleukin-12 antagonists as new therapeutic agents in inflammatory bowel disease. *Pathobiology*, *70*(3), 177. DOI: 10.1159/000068151
- Schroeder, K.W., Tremaine, W.J., Ilstrup, D.M., (1987). Coated oral 5-aminosalcylic acid therapy for mildly to moderately active ulcerative colitis. *N Eng J Med,* 317(26): 1625-1629.
- Schwarz, S. P., & Blanchard, E. B. (1991). Evaluation of a psychological treatment for inflammatory bowel disease. *Behaviour research and therapy*, *29*(2), 167-177.
- Seligman M., Learned Optimism, Vintage Books, New York, NY, USA, 2002.
- Serretti, A., Chiesa, A., Porcelli, S., Han, C., Patkar, A. A., Lee, S. J., ... & Pae, C. U. (2011). Influence of TPH2 variants on diagnosis and response to treatment in patients with major depression, bipolar disorder and schizophrenia. *Psychiatry research*, *189*(1), 26-32.

- Severs, M., Mangen, M. J., Van der Valk, M. E., Fidder, H. H., Dijkstra, G., van der Have, M., ... & Clemens, C. H. M. (2017). Smoking is associated with higher disease-related costs and lower health-related quality of life in inflammatory bowel disease. *Journal of Crohn's and Colitis*, *11*(3), 342-352. doi.org/10.1093/ecco-jcc/jjw160
- Sewitch, M. J., Abrahamowicz, M., Bitton, A., Daly, D., Wild, G. E., Cohen, A., … Dobkin, P. L. (2001). Psychological distress, social support, and disease activity in patients with inflammatory bowel disease. *The American Journal of Gastroenterology, 96(5), 1470–1479.* doi:10.1111/j.1572-0241.2001.03800.x
- Sgambato, D., Miranda, A., Ranaldo, R., Federico, A., & Romano, M. (2017). The role of stress in inflammatory bowel diseases. *Current pharmaceutical design*, *23*(27), 3997-4002. d oi.org/10.2174/1381612823666170228123357
- Shaw, M. H., Kamada, N., Warner, N., Kim, Y. G., & Nuñez, G. (2011). The ever-expanding function of NOD2: autophagy, viral recognition, and T cell activation. *Trends in immunology*, *32*(2), 73-79. doi.org/10.1016/j.it.2010.12.007
- Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The Development and Validation of a Structured Diagnostic Psychiatric Interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, 59(20), 22-33.
- Shivashankar, R., Tremaine, W. J., Harmsen, W. S., & Loftus Jr, E. V. (2017). Incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota from 1970 through 2010. *Clinical Gastroenterology and Hepatology*, *15*(6), 857-863. d oi.org/10.1016/j.cgh.2016.10.039

- Shouval, D. S., & Rufo, P. A. (2017). The role of environmental factors in the pathogenesis of inflammatory bowel diseases: a review. *JAMA pediatrics*, *171*(10), 999-1005. doi:10.1001/jamapediatrics.2017.2571
- Sibaja, M. D., Moreno, M. C., & Hesse, B. M. (2007). Protocolized cognitive-behavioural group therapy for inflammatory bowel disease. *Revista Espanola de Enfermedades Digestivas*, *99*(10), 593.
- Sifneos, P. E. (1973). The prevalence of 'alexithymic'characteristics in psychosomatic patients. *Psychotherapy and psychosomatics*, *22*(2-6), 255-262.
- Simrén, M., Axelsson, J., Gillberg, R., Abrahamsson, H., Svedlund, J., & Björnsson, E. S. (2002). Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *The American journal of gastroenterology*, *97*(2), 389-396.
- Singh, S., Graff, L. A., & Bernstein, C. N. (2009). Do NSAIDs, antibiotics, infections, or stress trigger flares in IBD?. *The American journal of gastroenterology*, *104*(5), 1298.
- Skinner, E. A. (1996). A guide to constructs of control. *Journal of personality and social psychology*, *71*(3), 549.
- Sonino, N., & Fava, G. A. (2012). Improving the concept of recovery in endocrine disease by consideration of psychosocial issues. *The Journal of Clinical Endocrinology & Metabolism*, *97*(8), 2614-2616.
- Spiller R, & Major G (2016). IBS and IBD - separate entities or on a spectrum? *Nat Rev Gastroenterol Hepatol*, 13:613-621.
- Spiller RC, Humes DJ, Campbell E, Hastings M, Neal KR, Dukes GE, Whorwell PJ. (2010). The Patient Health Questionnaire 12 Somatic Symptom scale as a predictor of

symptom severity and consulting behaviour in patients with irritable bowel syndrome and symptomatic diverticular disease. *Aliment Pharmacol Ther*, 32:811-20.

- Spitzer, RL, Kroenke, K, Williams, JB: Validation and utility of a self-report version of PRIME–MD: the PHQ Primary Care Study. Primary Care Evaluation of Mental Disorders Patient Health Questionnaire. JAMA 1999; 282:1737–1744 17. doi:10.1001/jama.282.18.1737
- Steed, H. (2019). Ulcerative colitis. *Medicine*, *in press*. doi.org/10.1016/j.mpmed.2019.03.001
- Steinhubl, S. R., Muse, E. D., and Topol, E. J. (2013). Can mobile health technologies transform health care? *JAMA,* 310, 2395–2396. doi:10.1001/jama.2013.281078
- Stevens, T. W., Matheeuwsen, M., Lönnkvist, M. H., Parker, C. E., Wildenberg, M. E., Gecse, K. B., & D'Haens, G. R. (2018). Systematic review: predictive biomarkers of therapeutic response in inflammatory bowel disease—personalised medicine in its infancy. *Alimentary pharmacology & therapeutics*, 48(11-12), 1213-1231.
- Svedlund, J., Sjodin, I., & Dotevall, G. (1988). GSRS – a clinical scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. *Digestive Diseases and Sciences*, 33, 129–134.
- Szigethy, E. V. A., Kenney, E., Carpenter, J., Hardy, D. M., Fairclough, D., Bousvaros, A., ... & DeMASO, D. R. (2007). Cognitive-behavioral therapy for adolescents with inflammatory bowel disease and subsyndromal depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(10), 1290-1298.
- Taché, Y., & Bernstein, C. N. (2009). Evidence for the role of the brain-gut axis in inflammatory bowel disease: depression as cause and effect?. *Gastroenterology*, *136*(7), 2058.

- Taylor, G. J., Bagby, M., & Parker, J. D. (1992). The Revised Toronto Alexithymia Scale: some reliability, validity, and normative data. *Psychotherapy and psychosomatics*, *57*(1-2), 34-41. doi.org/10.1159/000288571
- Taylor, G. J., Bagby, R. M., Ryan, D. P., Parker, J. D., Doody, K. F., & Keefe, P. (1988). Criterion validity of the Toronto Alexithymia Scale. *Psychosomatic medicine*, *50*(5), 500-509.
- Taylor, S. F., Phan, K. L., Decker, L. R., & Liberzon, I. (2003). Subjective rating of emotionally salient stimuli modulates neural activity. *Neuroimage*, *18*(3), 650-659.
- Timmerby, N., Austin, S. F., Ussing, K., Bech, P., & Csillag, C. (2016). Family psychoeducation for major depressive disorder–study protocol for a randomized controlled trial. *Trials*, *17*(1), 427.
- Torres, J., Mehandru, S., Colombel, J. F., & Peyrin-Biroulet, L. (2017). Crohn's disease. *The Lancet*, *389*(10080), 1741-1755. d oi.org/10.1016/S0140-6736(16)31711-1.
- Tzvetkov, M. V., Brockmöller, J., Roots, I., & Kirchheiner, J. (2008). Common genetic variations in human brain-specific tryptophan hydroxylase-2 and response to antidepressant treatment. *Pharmacogenetics and genomics*, *18*(6), 495-506.
- Uhlig, H. H., McKenzie, B. S., Hue, S., Thompson, C., Joyce-Shaikh, B., Stepankova, R., ... & Powrie, F. (2006). Differential activity of IL-12 and IL-23 in mucosal and systemic innate immune pathology. *Immunity*, *25*(2), 309-318. doi.org/10.1016/j.immuni.2006.05.017
- Ushijima, T., Nakajima, T., & Maekita, T. (2006). DNA methylation as a marker for the past and future. *Journal of gastroenterology*, *41*(5), 401-407. doi.org/10.1007/s00535-006-1846-6

- Van Der Flier, L. G., & Clevers, H. (2009). Stem cells, self-renewal, and differentiation in the intestinal epithelium. *Annual review of physiology*, *71*, 241-260. doi.org/10.1146/annurev.physiol.010908.163145
- Van der Sluis, M., De Koning, B. A., De Bruijn, A. C., Velcich, A., Meijerink, J. P., Van Goudoever, J. B., ... & Einerhand, A. W. (2006). Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. *Gastroenterology*, *131*(1), 117-129. doi.org/10.1053/j.gastro.2006.04.020
- van Langenberg, D. R., Simon, S. B., Holtmann, G. J., & Andrews, J. M. (2010). The burden of inpatient costs in inflammatory bowel disease and opportunities to optimize care: a single metropolitan Australian center experience. *Journal of Crohn's and Colitis*, *4*(4), 413-421.
- Vaughn, C., Leff, J., & Sarner, M. (1999). Relatives' expressed emotion and the course of inflammatory bowel disease. Journal of Psychosomatic Research, 47(5), 461-469.
- Ventham, N. T., Kennedy, N. A., Nimmo, E. R., & Satsangi, J. (2013). Beyond gene discovery in inflammatory bowel disease: the emerging role of epigenetics. *Gastroenterology*, *145*(2), 293-308. doi.org/10.1053/j.gastro.2013.05.050
- Verdejo, C., Hervías, D., Roncero, Ó., Arias, Á., Bouhmidi, A., Lorente, R., ... & Lucendo, A. J. (2018). Fecal calprotectin is not superior to serum C-reactive protein or the Harvey–Bradshaw index in predicting postoperative endoscopic recurrence in Crohn’s disease. European journal of gastroenterology & hepatology, 30(12), 1521-1527.
- Verissimo, R., Mota-Cardoso, R., & Taylor, G. (1998). Relationships between alexithymia, emotional control, and quality of life in patients with inflammatory bowel disease. *Psychotherapy and psychosomatics*, *67*(2), 75-80.

- Verissimo, R., Taylor, G. J., & Bagby, R. M. (2000). Relationship between alexithymia and locus of control. *New Trends in Experimental and Clinical Psychiatry*, *16*(1/4), 11-16.
- Vidal, A., Gómez-Gil, E., Sans, M., Portella, M. J., Salamero, M., Piqué, J. M., & Panés, J. (2008). Health-related quality of life in inflammatory bowel disease patients: the role of psychopathology and personality. *Inflammatory Bowel Diseases*, *14*(7), 977-983.
- Vivan, T. K., Santos, B. M., & dos Santos, C. H. M. (2017). Quality of life of patients with inflammatory bowel disease. *Journal of Coloproctology*, *37*(4), 279-284.
- von Wietersheim, J., & Kessler, H. (2006). Psychotherapy with chronic inflammatory bowel disease patients: a review. *Inflammatory bowel diseases*, 12(12), 1175-1184.
- Voskuil, M. D., Bangma, A., Weersma, R. K., & Festen, E. A. M. (2019). Predicting (side) effects for patients with inflammatory bowel disease: The promise of pharmacogenetics. World journal of gastroenterology, 25(21), 2539.
- Walker, J. R., Ediger, J. P., Graff, L. A., Greenfeld, J. M., Clara, I., Lix, L., ... & Bernstein, C. N. (2008). The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *The American journal of gastroenterology*, *103*(8), 1989.
- Wiklund, I. K., Fullerton, S., Hawkey, C. J., Jones, R. H., Longstreth, G. F., Mayer, E. A., et al. (2003). An irritable bowel syndrome-specific symptom questionnaire: development and validation. Scandinavian Journal of Gastroenterology, 38, 947e954.
- Wilkinson, B., Trick, L., Knight, A., Valton, V., Goodhand, J., Kennedy, N. A., ... & Roiser, J. P. (2019). Factors associated with depression in people with inflammatory bowel disease: The relationship between active disease and biases in neurocognitive processing. *Neurogastroenterology & Motility*, *31*(8), 1-11.

- World Health Organization, Construction in Basic Documents, World Health Organization, Geneva, Switzerland, 1948.
- Zhang, Y. Z., & Li, Y. Y. (2014). Inflammatory bowel disease: pathogenesis. *World journal of gastroenterology: WJG*, *20*(1), 91.
- Zigmond, AS, Snaith, RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67: 361–70. Doi: 10.1111/j.1600-0447.1983.tb09716.x.